Total Syntheses of (–)-Fragin and Valdiazen, and Synthetic Studies Towards Complex Neuritogenic Terpenoids

Inauguraldissertation

zur Erlangung der Würde eines Doktors der Philosophie

vorgelegt der
Philosophisch-Naturwissenschaftlichen Fakultät
der Universität Basel

von

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Basel, 2017

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät
auf Antrag von

Prof. Dr. Karl Gademann

Prof. Dr. Andreas Pfaltz

Basel, den 21. Juni 2016

Prof. Dr. Jörg Schibler
- Dekan -

Für Vidya
und meine Familie

Discovery is seeing what everybody else has seen,
and thinking what nobody else has thought.

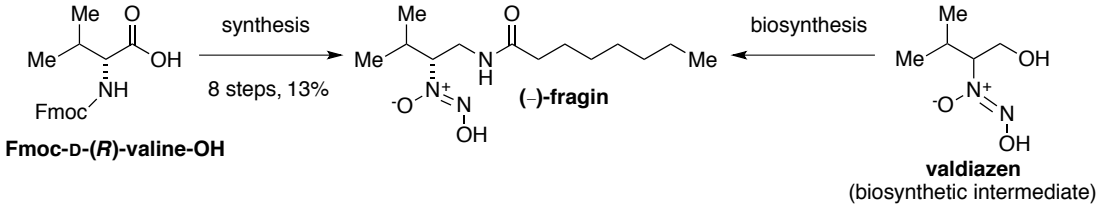
Albert Szent-Gyorgyi (1893 – 1986)

Table of Content

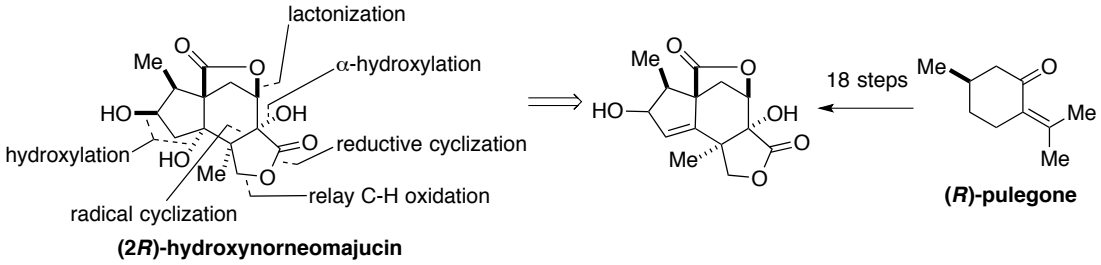
Abstract

This thesis is divided in five chapters, highlighting natural products as valuable sources for the treatment of mankind diseases. The **first chapter** gives a general introduction into the early research and development of natural products and their history as suitable drugs in the past time. For a long time, a common strategy was the use of small molecules. Often, natural products proved to be valuable sources or were the initial step or the fundament for the development of drugs.

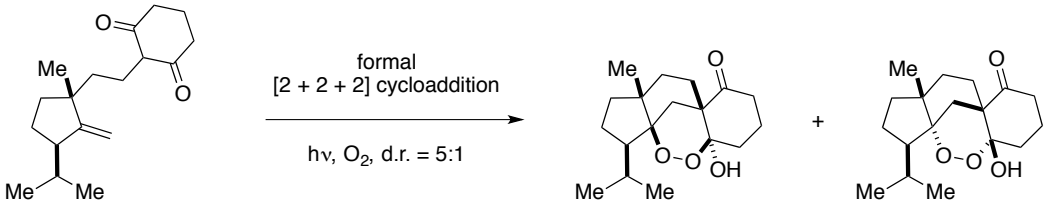
The **second chapter** is based on a long-known but poorly investigated natural product named fragin. The structurally fascinating and rare diazeniumdiolate moiety captured our attention. An enantioselective synthesis was elaborated to clarify the unknown stereogenic center. Furthermore, a racemic intermediate in the biosynthesis of fragin, named valdiazen, was isolated and confirmed *via* chemical synthesis. SAR-studies on fragin identified the activity-driven part of the molecule and the influence of the substituents on the antibacterial activity.



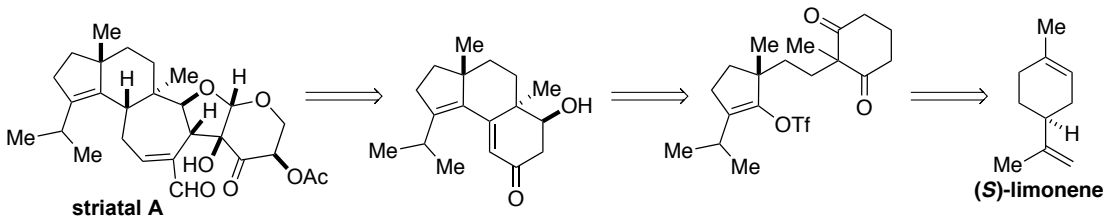
Neurodegenerative diseases are affecting increasing numbers of people worldwide and will become a serious problem for our health system. The **third chapter** shows the current state of the art in neurodegenerative disease treatment and how chemists were providing small molecules with potent activity to this research field. The genus *Illicium* is known to deliver natural products with potent neurite outgrowth inducing activity. One of these molecules is (2*R*)-hydroxynorneomajucin, which comprises a rare *nor*-type structure. We aimed to provide a total synthesis and SAR-studies to this synthetically challenging scaffold. An advanced intermediate was successfully synthesized in 18 steps.



Malaria is one of the deadliest diseases since ages and the uprising problem of strain resistance makes the future outlook even less promising. The **fourth chapter** describes the serendipity of a reaction to access novel endoperoxides. The formation of the endoperoxidal structure was first achieved in the presence of pure oxygen and further improved by the addition of a catalyst to induce this formal [2 + 2 + 2] cycloaddition. SAR-studies on these potent antimalarials provided a first insight into the active parts of the compounds.



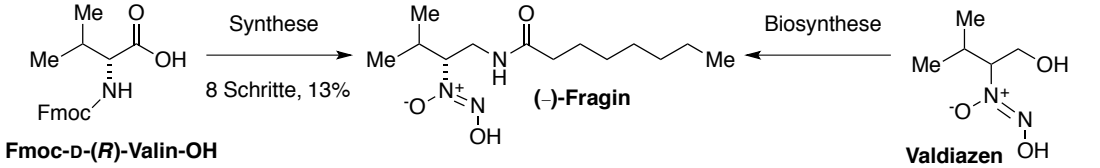
The **fifth chapter** is dedicated to the field of antibiotics research. Natural products showed their value in the early development steps of antibiotics, but became then an almost forgotten research field. Nevertheless, emerging bacterial strain resistance becomes more of a problem worldwide, and the discovery of novel antibiotics is desperately needed. The chapter reports on our synthetic efforts towards the antibiotic striatal A. The goal of this project is to provide a synthetic entry into the striatal family. However, the first attempt was not fruitful and led to several problems such as low yields or by-product formation. A new strategy was evaluated, that targets the synthesis of a bis-diazoketone precursor to form the tricyclic core structure.



Zusammenfassung

Die hier zusammengestellte wissenschaftliche Arbeit ist in fünf Kapitel unterteilt und beschreibt Naturstoffe als wertvolle Ausgangssubstrate zur Behandlung von verschiedenen Krankheitsbildern. **Kapitel eins** beinhaltet eine generelle Einleitung und gibt erste Einblicke in die Geschichte der Entwicklung moderner Wirkstoffe und den daraus resultierenden Therapien für diverse Krankheiten. Eine Strategie war die Verwendungen von kleinen Molekülen, wie zum Beispiel Naturstoffen. Diese Stoffe waren oftmals der erste Schritt für die weitere Entwicklung einer Therapie.

Kapitel zwei basiert auf einem lange bekannten, jedoch kaum beachteten Naturstoff namens Fragin. Speziell die funktionelle Gruppe, ein Diazeniumdiolat, macht diesen Naturstoff besonders interessant. Eine enantioselektive Synthese von beiden Fragin Enantiomeren wurde erarbeitet um das unbekannte Chiralitätszentrum zu bestimmen. Zusätzlich wurde Valdiazen, eine biosynthetische Zwischenstufe von Fragin isoliert und die Struktur mittels chemischer Synthese vollumfänglich bestätigt. SAR-Studien von Fragin identifizierten desweiteren den aktiven Teil des Moleküls, sowie den Einfluss der Substituenten auf die antibakterielle Aktivität.

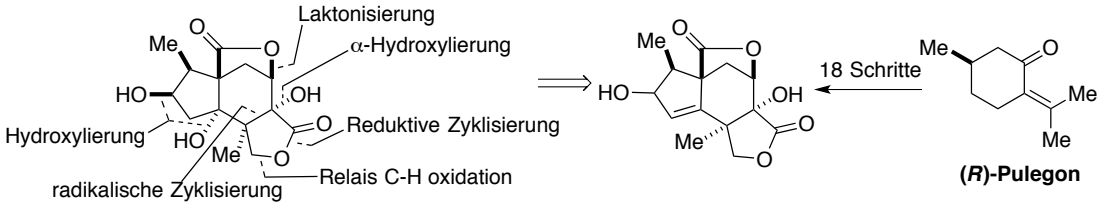


Fmoc-D-(*R*)-Valin-OH

Valdiazen (biosynthetisches Intermediat)

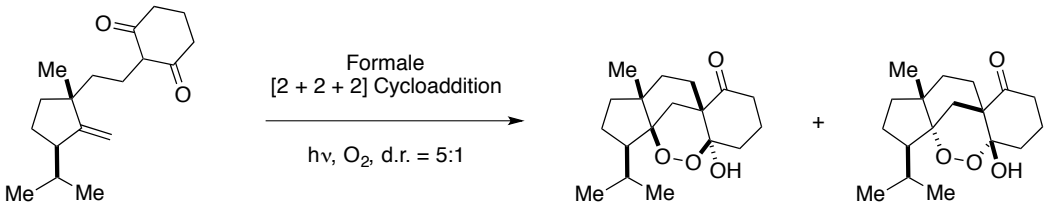
Neurodegenerative Krankheiten betreffen eine zunehmende Anzahl an Personen in unserer Gesellschaft und werden daher in den kommenden Jahren grosse Auswirkungen auf unser Gesundheitssystem haben. **Kapitel drei** zeigt den aktuellen Forschungsstand von Nervenkrankheiten und wie Chemiker ihren Beitrag mittels wirksamen kleinen Molekülen beisteuern. Die Gattung *Illicium* ist bekannt für ihre Vielfalt an Neuritenwachstum-fördernden Molekülen. Eines dieser Natustoffe ist (2*R*)-Hydroxynorneomajucin, welches eine seltene *nor*-Struktur besitzt. Ziel unserer Arbeit ist dessen Totalsynthese

um SAR-Studien zu ermöglichen. Eine Zwischenstufe konnte in 18 Schritten erfolgreich synthetisiert werden.



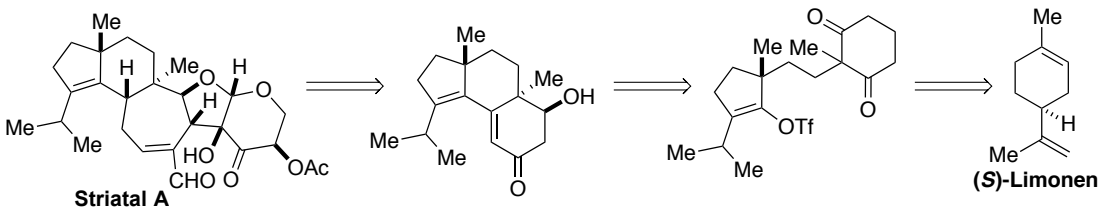
(2*R*)-Hydroxynorneomajucin **(*R*)-Pulegon**

Malaria ist seit Jahren eine der tödlichsten Krankheiten weltweit und aufkommende Resistenzen gegen heutige Therapien werden zunehmend problematisch. **Kapitel vier** beschreibt die zufällige Entdeckung einer Reaktion zur Herstellung neuer Endoperoxide. Die Bildung der Endoperoxid-Struktur wurde mittels Sauerstoff über eine formale [2 + 2 + 2] Cycloaddition gebildet und dann weiter optimiert durch Zugabe eines Katalysators. SAR-Studien dieser Antimalaria-aktiven Moleküle gaben einen ersten Einblick in die aktiven Teile des Moleküls.



Antimalaria aktive Endoperoxide

Das **fünfte Kapitel** ist der Antibiotika Forschung gewidmet. Naturstoffe haben Ihren Wert und Einfluss zu Beginn der Antibiotika Ära gezeigt. Wegen der stark aufkommenden Resistenz von Bakterien gegenüber Antibiotika, wird ein Nachschub an neuen Antibiotika dringender denn je benötigt. Das Kapitel beinhaltet unsere synthetischen Arbeiten zur Totalsynthese des Antibiotikums Striatal A. Erste Versuche basierend auf der Totalsynthese eines kürzlich synthetisierten Naturstoffes in unserer Gruppe konnten leider nicht auf das neue Substrat übertragen werden. Daher wurde eine neue Strategie evaluiert, welche eine Bis-Diazoketon Zwischenstufe beinhaltet um die dreizyklische Grundstruktur zu erhalten.



Striatal A **(*S*)-Limonen**

1 General Introduction – Dawn of a New Age of Natural Products Drug Discovery?

Modern technology and pharmaceutical drugs have changed the life of today's society. This progress has been greatly influenced by chemistry-based inventions and in the last decade, several eras are referred to as the "Golden Ages" or "Golden Eras" for chemistry. In many cases, the discovery of natural products initiated a "Golden Era" and natural products continue to influence science until today.[1]

The golden era of antibiotics discovery (1940 – 1960) had a huge impact on the health system (Figure 1.1).[2] Sir Alexander Fleming discovered one of the first antibiotics already a few years earlier, in 1929.[3] It took a few years for Fleming's penicillin (**1.1**) to become world's most famous antibiotic. A research article on penicillin's activity in 1940 begun with the words *"In recent years interest in chemotherapeutic effects has been almost exclusively focused on the sulphonamides and their derivatives. There are, however, other possibilities, notably those connected with naturally occurring substances"* and landmarked the era of natural products as antibiotics (Figure 1.1).[4] In this era, numerous antibiotic natural products such as tetracycline (**1.2**) (Pfizer, 1952), erythromycin (**1.3**) (Eli Lilly, 1949) and vancomycin (**1.4**)[5] (Eli Lilly, 1952) were discovered and antibiotic nature-inspired drugs were synthesized. The golden era ended along with the upcome of increased resistance of pathogens towards several antibiotics. The work on novel and potent antibiotics was not fruitful anymore as resistance became a serious problem and novel antibiotics were, and still are, saved as last-line drugs.

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1 D. D. Baker, M. Chu, U. Oza, V. Rajgarhia, *Nat. Prod. Rep*. **2007**, *24*, 1225.

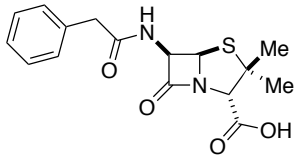
2 P. M. Wright, I. B. Seiple, A. G. Myers, *Angew. Chem. Int. Ed*. **2014**, *53*, 8840.

3 A. Fleming, *Br. J. Exp. Pathol*. **1929**, *10*, 226.

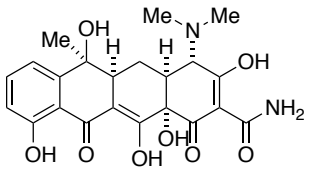
4 E. Chain, W. Florey, A. D. Gardner, N. G. Heatley, M. A. Jennings, J. Orr-Erwing, A. G. Sanders, *Lancet* **1940**, *2*, 226.

5 D. H. Williams, B. Bardsley, *Angew. Chem. Int. Ed*. **1999**, *38*, 1172.

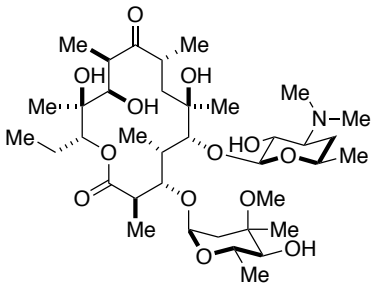
Thus, pharmaceutical companies gave up on their research in finding more powerful treatment methods. However, a strong research for novel antibiotics is highly desirable.



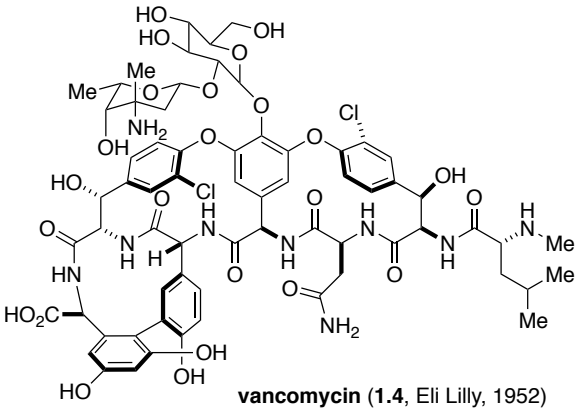
penicillin (**1.1**, Fleming 1929)



tetracycline (**1.2**, Pfizer 1952)



erythromycin (**1.3**, Eli Lilly 1949)



vancomycin (**1.4**, Eli Lilly, 1952)

Figure 1.1: Famous antibiotics in the "golden era of antibiotics discovery".

The years 1960 – 1970 can be regarded as the golden era of chemotherapy.[6] In the beginning, the field of anticancer treatment was dominated by removal of the cancer by surgery or radiology. However, due to onset of metastasis in some cancer types, surgery or complete radiology was not always suitable and thus, small molecule drugs came into the focus of researchers. The discovery of the first anticancer agents (nitrogen mustard (**1.5**)[7] and antifolates (folic acid (**1.6**) and methotrexate (**1.7**)[8]) begun already in the 1940's (Figure 1.2). The breakthrough for small molecules in anticancer treatment goes back to researcher from Eli Lilly, who found active anticancer agents in the plant of *Vinca rosea*.[9] These molecules showed also strong

6 B. A. Chabner, T. G. Roberts, jr., *Nature Reviews Cancer* **2005**, *5*, 65.

7 H. A. A. M. Dirven, B. van Ommen, P. J. van Bladeren, *Chem. Res. Toxicol*. **1996**, *9*, 351.

8 N. Gonen, Y. G. Assaraf, *Drug Resistance Updates* **2012**, *15*, 183.

9 I. S. Johnson, J. G. Armstrong, M. Gorman, J. P. Burnett, jr. *Cancer Res*. **1963**, *23*, 1390.

activity against onchocerciasis (river blindness) and lymphatic filariasis (elephantiasis). One of the active principles was vinblastine (**1.8**) along with other members of the *Vinca* alkaloid family.

Much earlier, Furth and Kahn demonstrated the danger of cancer by showing that a single cancer cell was sufficient to kill a mouse.[10] Further studies showed that monotherapy was mostly not effective enough. This observation was then associated to hypothesis that an anticancer agent only kills a fraction of all cancer cells and surviving cancer cells are still able to grow. Therefore, on one hand, multiple treatment dosages and combination of therapies are necessary, and on the other hand, a successful treatment is strongly dependent on the initial cancer cell number.[11] By the end of 1970, several cancer types (childhood leukemia, Hodgkin's disease) could be cured or at least showed promising results in terms of remission. The value of small molecules in chemotherapy as anticancer agents could be fully confirmed during this golden era of chemotherapy.

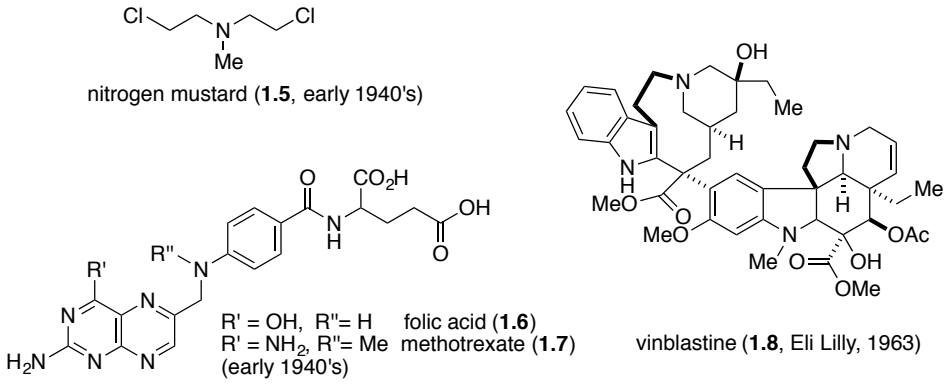


Figure 1.2: Famous chemotherapeutic agents in the "golden age of chemotherapy".

[10] J. Furth, M. C. Kahn, *Am. J. Cancer* **1937**, *31*, 276.

[11] V. T. DeVita, jr., E. Chu, *Cancer Res*. **2008**, *68*, 8643.

In the years of 1980 to present, novel techniques such as high-throughput screening methods and combinatorial chemistry came up, which allowed the broad screening of a vast number of molecules as well as a fast analysis of structure-activity relationship.[12] Classical natural product discovery became less interesting and as a consequence, the natural product section in most pharmaceutical companies was down-sized or completely erased. However, a recent survey of launched marketed drugs in the year 2000 showed that 8 out of 29 molecules are derived from natural products and the authors came to the conclusion that high-throughput screening did not have a significant impact on the finally launched structure.[13]

The early golden ages in chemistry were strongly dependent on industrial partners, that directly influenced and developed novel techniques and molecules for commercial use. Nevertheless, a new golden era might arise, which is more needed than before. As possible landmark might act the 2015's Nobel Prize in Physiology or Medicine, which was dedicated to the field of natural products and their contribution to mankind's health system improvement. The Nobel laureate Youyou Tu was searching for a new treatment against malaria and found the anti-malarial agent artemisinin (**1.9**) in the plant *Artemisia annua* (Figure 1.3).[14] This natural product significantly contributed to the prevention of malaria by reducing the patient's mortality numbers suffering from malaria. William C. Campbell and Satoshi Omura were awarded for the discovery of avermectins (represented by avermectin B1 (**1.10**) and an improved analogue of it named ivermectin (**1.11**), Figure 1.3).[14] These molecules showed strong activity against onchocerciasis (river blindness) and lymphatic filariasis (elephantiasis).

[12] J. G. Lombardino, J. A. Lowe, III, *Nature Reviews Drug Discovery* **2004**, *3*, 853.

[13] a) J. R. Proudfoot, *Bioorganic & Medicinal Chemistry Letters* **2002**, *12*, 1647; b) M. S. Butler, *J. Nat. Prod*. **2004**, *67*, 2141.

[14] B. Shen, *Cell* **2015**, *163*, 1297.

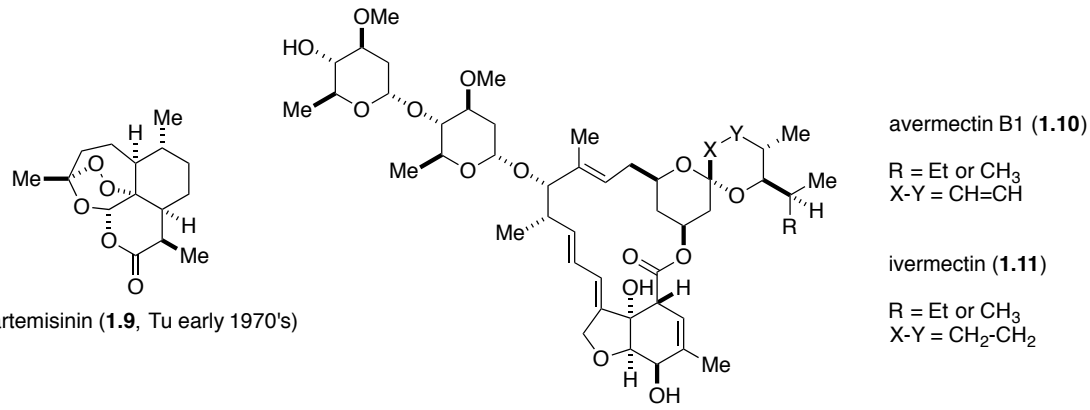


Figure 1.3. Natural products for which Youyou Tu as well as William C. Campbell and Satoshi Omura were awarded the Nobel Prize in Physiology or Medicine 2015.

Omura described natural products as "*splendid gifts*" from nature,[15] and it is rather obvious that natural products are main actors in the development of pharmaceutical drugs and reliefs. All these examples show that the best chemist in the world is still nature itself.

[15] S. Omura, *Tetrahedron* **2011**, *67*, 6420.

2 Enantioselective Total Syntheses and SAR-Studies on the antifungal metabolite (–)-Fragin and Valdiazen

2.1 Introduction

2.1.1 Nitrogen Discovery and Synthetic Utility in Industrial Processes

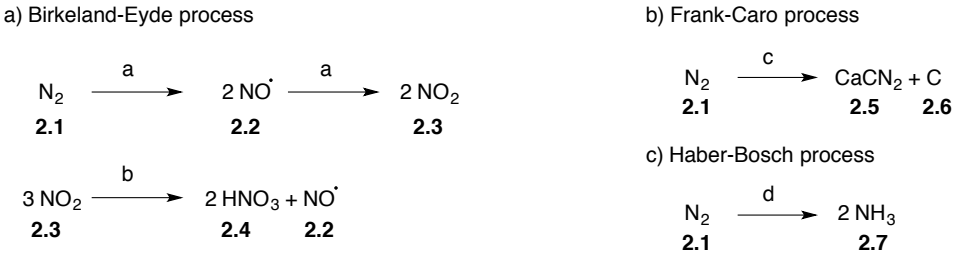
Nitrogen (N_2, **2.1**) was discovered in 1772 by the physician Daniel Rutherford by analyzing the composition of air, which consists of around 78% N_2 **2.1**. He and other researcher recognized that N_2 **2.1** was inert and often referred as “burnt air” or azote (from the greek “lifeless”). In 1870, Jean-Antoine Chaptal called it nitrogène from the greek words “nitron genes“ (nitrite forming), due to the fact that “N_2” was found in potassium nitrate (“nitrum”).[16] An entrance to nitrogen containing chemicals derived from N_2 **2.1** gas was achieved by the Birkeland-Eyde process (Scheme 2.1a). Nitrogen was passed trough an electric arc (>3000 °C) with oxygen to form nitric oxide ($NO^{\bullet}$, **2.2**), which is further oxidized to nitrogendioxide (NO_2, **2.3**) and afterwards treated with water to form nitric acid (HNO_3, **2.4**).[17,18] The Frank-Caro process (also called cyanamide process) was the first commercial synthesis, which used nitrogen (**2.1**). It was reacted with calcium carbide (CaC_2) to yield cyanamide (**2.5**) and charcoal (**2.6**) as the product (Scheme 2.1b).[17] However high temperatures were required for the reaction and small quantities are obtained. An alternative and more successful method is the Haber-Bosch process (Scheme 2.1c), which uses nitrogen (**2.1**) and hydrogen gas in combination with a catalyst (original osmium-based, nowadays ironoxide based) to form ammonia (NH_3, **2.7**).[17] The process was used as a nitrogen feedstock for the

[16] M. E. Weeks, *J. Chem. Educ.* **1934**, *11*, 101.

[17] A. S. Travis, *The Synthetic Nitrogen Industry in World War I It’s Emergence and Expansion* **2015**, 1st ed., Springer, Heidelberg.

[18] E. A. Ainscough, A. M. Brodie, *J. Chem. Educ.* **1995**, *72*, 686.

agriculture and had therefore an extreme influence on society growth and health.[19]



Scheme 2.1: Initial nitrogen (**2.1**) fixation approaches. a) O_2; b) O_2, H_2O; c) CaC_2; d) H_2, cat.

2.1.2 Nature's Nitrogen Sources

In nature, nitrogen can be found in a variety of organic molecules such as alkaloids, amino acids and proteins derived from amino acids. The simplest nitrogen-species may be nitric oxide (NO•, **2.2**, uncharged radical species).[20] NO• **2.2** is a gas and quite stable in its pure form, but gets easily oxidized in the presence of air.[21] NO• **2.2** is an important neurotransmitter in living beings and for its discovery, the scientists Robert F. Furchgott, Louis J. Ignarro and Ferid Murad were awarded with the Nobel Prize in Physiology or Medicine in 1998 entitled "*for their discoveries concerning nitric oxide as a signaling molecule in the cardiovascular system*".[22] The small size and uncharged character of the radical NO• **2.2** allows a diffusion into cells and therefore allows interactions over a wider range with synapses and neurons compared to other neurotransmitters (acetylcholine, GABA, glutamate, glycin). NO• **2.2** is produced *via* an endogenous pathway by the enzyme nitric oxide synthase (NOS).[23] The enzyme converts L-arginine (**2.8**) *via* the hydroxylated intermediate *N*-hydroxy-L-arginine (**2.9**) to L-citruline (**2.10**) and NO• **2.2** is released (Scheme 2.2).[24]

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19 V. Smil, *World Agriculture* **2011**, *2*, 9.

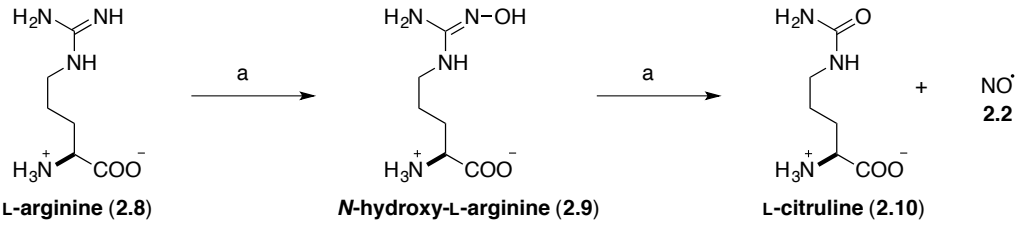
20 a) R. F. Furchgott, J. V. Zawadzki, *Nature* **1980**, *288*, 373; b) R. M. J. Palmer, A. G. Ferrige, S. Moncada, *Nature* **1987**, *327*, 524.

21 C. S. Howard, F. Daniels, *J. Phys. Chem*. **1958**, *62*, 360.

22 R. SoRelle, *Circulation* **1998**, *98*, 2365.

23 R. G. Knowles, S. Moncada, *Biochem. J.* **1994**, *298*, 249.

24 a) J. B. Hibbs, Jr., R. T. Traintor, Z. Vavrin, *Science* **1987**, *235*, 473; b) P. G. Jorens, P. A. Vermeire, A. G. Herman, *Eur. Respir. J.* **1993**, *6*, 258; c) D. J. Stuehr, *Biochim. Biophys. Acta* **1999**, *1411*, 217.



Scheme 2.2: Enzymatic NO-generation from L-arginine.[25] a) NADPH, O_2.

The main biological action of $NO^{\bullet}$ **2.2** is the activation of the guanylate cyclase, which synthesizes cyclic guanosine monophosphate (cGMP), known as a second messenger (signal transmitter in the cell). Other pathways involves the direct conversion of $NO^{\bullet}$ **2.2** to form reactive nitrogen species (RNS sometimes refers as RNI, reactive nitrogen intermediates),[26] and are related to their oxygen analogues ROS (reactive oxygen species).[27] Known intermediates are NO^+ **2.11**, NO^- **2.12**, N_2O_3 **2.13**, NO_2 **2.3**, NO_2^- **2.14**, NO_3^- **2.15**, $OONO^-$ **2.16**, and metal-nitrosyl adducts **2.17**. Oxidation of $NO^{\bullet}$ **2.2** forms nitrosonium (NO^+,**2.11**), which can react with nucleophiles such as R-OH **2.18**, R-SH **2.19** and amines **2.20** to form their nitrosylated species **2.21** – **2.24**. An one electron reduction forms nitroxyl-anion (NO^-, **2.12**), which converts under physiological conditions to N_2O **2.25** shown in Scheme 2.3.

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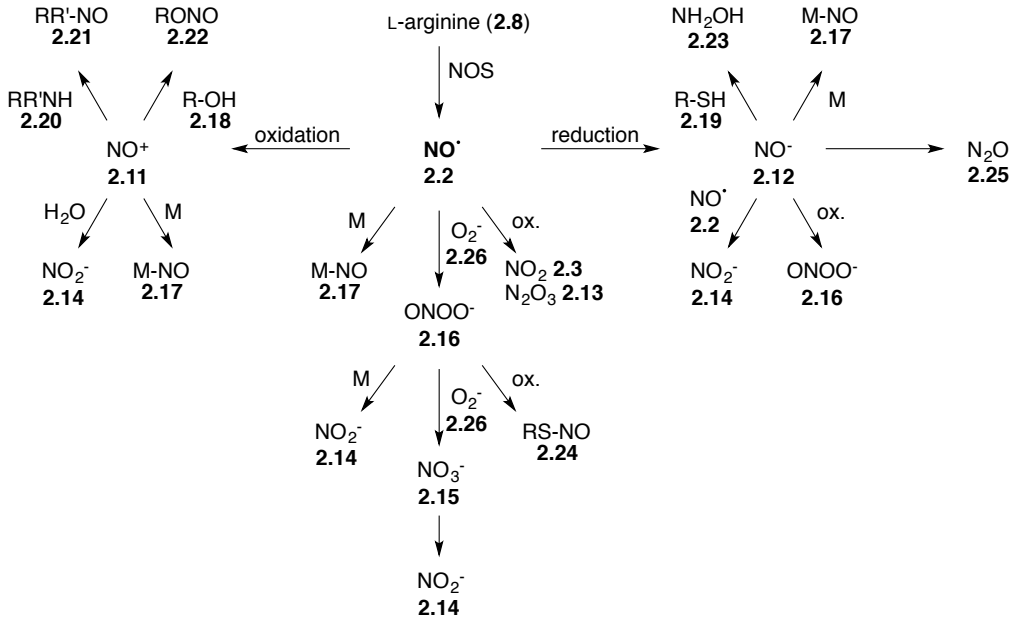
[25] T. B. Cai, P. G. Wang, A. A. Holder, *NO and NO Donors, in Nitric Oxide Donors: For Pharmaceutical and Biological Applications* **2005**, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

[26] a) C. Bogdan, M. Röllinghoff, A. Diefenbach, *Curr. Opin. Immunol* **2000**, *12*, 54; b) C. Nathan, M. U. Shiloh, *Proc. Natl. Acad. Sci.* **2000**, *97*, 8841.

[27] a) T. Rahman, I. Hosen, M. M. Towhidul Islam, H. U. Shekhar, *Advances in Bioscience and Biotechnology* **2012**, *3*, 997; b) B. D'Autréaux, M. B. Toledano, *Nat. Rev. Mol. Cell Biol.* **2007**, *8*, 813.



Scheme 2.3: Biological synthesis of NO• **2.2** and related oxidation and reduction pathways (M = metal; ox. = O_2).[25]

Theses reactive species have very interesting and biological important effects on infections, inflammation[28] or erectile disfunction.[29]

Nitroxyl-anion (NO^-, **2.12**, Scheme 2.3) is under physiological conditions a highly electrophilic species, which can be attacked by nucleophiles such as thiols **2.19** (*N*-acetyl-L-cysteine, dithiothreitol).[30] Nitroxyl (NO^-, **2.12**) is regarded as potent vasorelaxant and potential treatment for heart failure.[31] Peroxynitrites ($ONOO^-$, **2.16**) are formed from NO• **2.2** and superoxide (O_2^-, **2.26**).[32] A wide range of biological activities is associated to peroxynitrites **2.16** such as apoptosis inducer, calcium dysregulation, DNA mutation or mitochondrial dysfunction.[33]

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28 C. Nathan, *J. Clin. Invest*. **1997**, *100*, 2417.

29 a) A. L. Burnett, *Int. J. Impot. Res.* **2004**, *16*, 15; b) *J. Clin. Hypertens.* **2006**, *8*, 53.

30 W. Flores-Santana, D. J. Salmon, S. Donzelli, C. H. Switzer, D. Basudhar, L. Ridnour, R. Cheng, S. A. Glynn, N. Paolocci, J. M. Fukuto, K. M. Miranda, D. A. Wink, *Antioxid. Redox Signal.* **2011**, *14*, 1659.

31 N. Paolocci, M. I. Jackson, B. E. Lopez, K. Miranda, C. G. Tochetti, D. A. Wink, A. J. Hobbs, J. M. Fukuto, *Pharmacol. Ther.* **2007**, *113*, 442.

32 a) P. Pacher, J. S. Beckman, L. Liaudet, *Physiol. Rev*. **2007**, *87*, 315; b) L. M. Slosky, T. W. Vanderah, *Expert Opin. Ther. Patens* **2015**, *25*, 443.

33 C. Szabó, H. Ischiropoulos, R. Radi, *Nat. Rev. Drug Discov.* **2007**, *6*, 663.

2.1.3 Nitrogen Containing Structure Motifs

An important class of nitrogen containing functional group is the hydroxamic acid (**2.27**, Figure 2.1). They are structurally related to amides, but with an additional hydroxy function on the nitrogen moiety. This structural change features in the ability to complex several cations,[34] but mostly known to chelate Fe(III)-ions and therefore being siderophores.[35] The synthesis of hydroxamic acids is normally achieved by the condensation of a carbon acid or ester with hydroxylamine.[36]

Prominent representators of this functional group are ferrichrome **2.28**[37] and suberoylanilide hydroxamic acid (SAHA, **2.29**), depicted in Figure 2.1. A short synthesis was reported for SAHA **2.29**.[38]

SAHA **2.29** is used in cancer treatment,[39] where it is acting as a histone deacetylase inhibitor (HDAC inhibitor, IC_{50} = 0.86 nM). Two of three HDAC classes are zinc-dependent and studies showed that SAHA **2.29** binds to zinc metal in the HDAC catalytic site.[40] This mode of action results in a higher concentration of acetylated proteins and histones, finally leading to cell cycle arrest and apoptosis.[41]

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34 Y. K. Agrawal, *Russian Chem. Rev.* **1979**, *48*, 948.

35 a) R. Saha, N. Saha, R. S. Donofrio, L. L. Bestervelt, *J. Basic Microbiol*. **2013**, *53*, 303; b) S. Sah, R. Singh, *Agriculture (Polnohospodárstvo)* **2015**, *61*, 97; c) S. S. Ali, N. N. Vidhale, *Int. J. Curr. Microbiol. App. Sci.* **2013**, *2*, 303.

36 a) H. L. Yale, *Chem. Rev*. **1943**, *33*, 209; b) L. Bauer, O. Exner, *Angew. Chem. In. Ed*. **1974**, *13*, 376.

37 a) G. Müller, B. F. Matzanke, K. N. Raymond, *J. Bacteriol.* **1984**, *160*, 313; b) M. Hannauer, Y. Barda, G. L. A. Mislin, A. Shanzer, I. J. Schalk, *J. Bacteriol.* **2010**, *192*, 1212.

38 L. K. Gediya, P. Chopra, P. Purushottamachar, N. Maheshwari, V. C. O. Njar, *J. Med. Chem*. **2005**, *48*, 5047.

39 M. Duvic, *Hematology Meeting Reports* **2008**, *2*, 39.

40 P. A. Marks, R. A. Rifkind, V. M. Richon, R. Breslow, T. Miller, W. K. Kelly, *Nature* **2001**, *1*, 194.

41 V. M. Richon, *Br. J. Cancer* **2006**, *95*, 2.

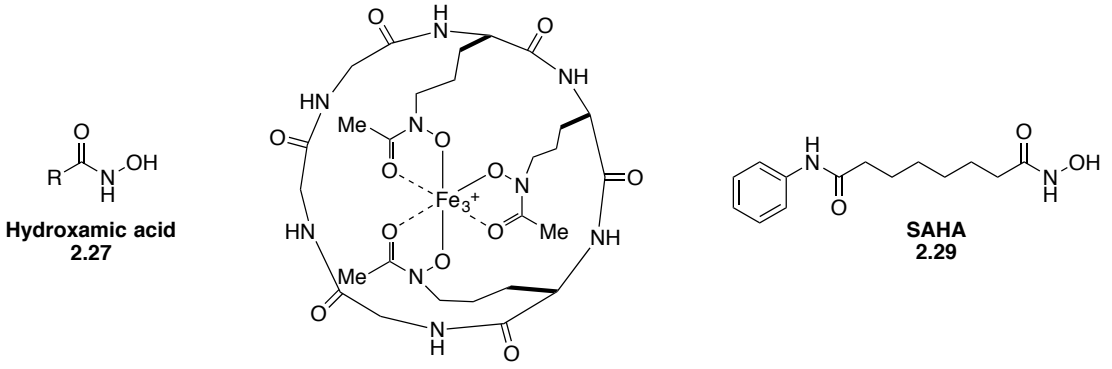


Figure 2.1: Hydroxamic acid containing molecules.

Similar chemical and biological properties were found for diazeniumdiolates **2.30** (Figure 2.2, left). The diazeniumdiolate functional group was first described by Davy in 1802.[42] This unique functional group consists of two nitrogen and two oxygen. The term diazeniumdiolate is derived from "diazen", which represents the N=N functional group. The tautomeric form is referred as *N*-nitrosohydroxylamine **2.31**. Crystal structure analysis revealed that the diazeniumdiolate **2.30** is present. The oxygen atoms are further distinguished based on their alkylating pattern in O^1 **2.32** and O^2 **2.33** (Figure 2.2, left), which have an effect on their stability, especially on their NO-releasing properties. The diazeniumdiolate species is further distinguished by the attached residue such as oxygen- **2.34**, nitrogen- **2.35** and carbon-containing diazeniumdiolate **2.36** (Figure 2.2, right). The main aspects of diazeniumdiolates **2.30** are covered in the review of Hrabie and Keefer.[25,43]

[42] H. Davy, *Bibl. Br. Sci. Arts* **1802**, *20*, 350.

[43] J. A. Hrabie, L. K. Keefer, *Chem. Rev*. **2002**, *102*, 1135.

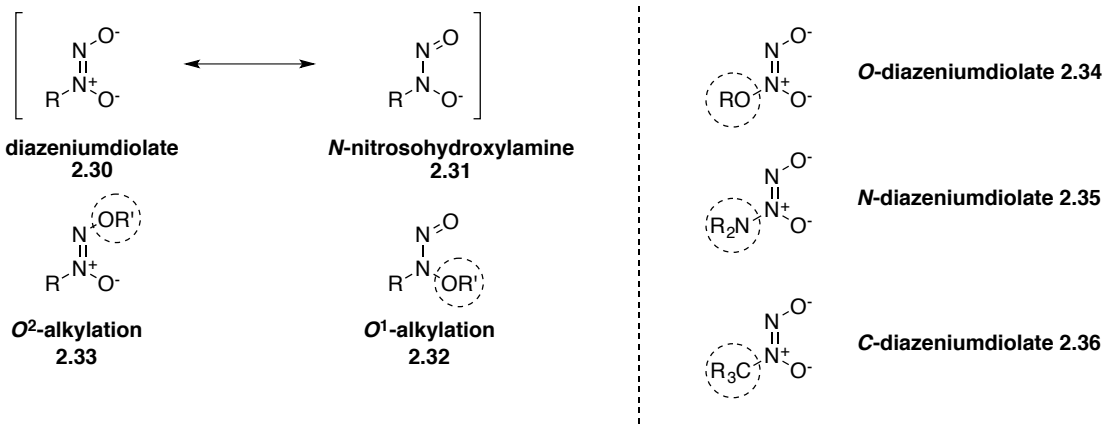
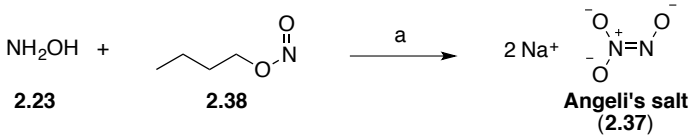


Figure 2.2: Diazeniumdiolate nomenclature, *O*-alkylation pattern and different diazeniumdiolate species.

Diazeniumdiolates **2.30** are potential NO• **2.2** releaser and have found numerous application in cancer treatment and other fields of drug research. Their differentiation, structures and biological profiles are discussed in the following section.

O-Diazeniumdiolates **2.34** are rarely described and the most known compound is Angeli's salt (**2.37**, also known as OXINO) discovered by the Italian chemist Angelo Angeli.[44] The synthesis is derived from hydroxylamine **2.23** and butylnitrite **2.38** as shown in Scheme 2.4.



Scheme 2.4: Synthesis of Angeli's salt (**2.37**).[45] a) NaOH, MeOH.

Experimental[46] and quantum mechanical calculations[47] revealed that the decomposition of Angeli's salt (**2.37**) is pH dependent. At a lower pH < 4, the N^2-oxygen-moiety is preferentially protonated and releases H_2O and N_2O **2.25**

[44] A. Angeli, *Gazz. Chim. Ital*. **1896**, *26*, 17.

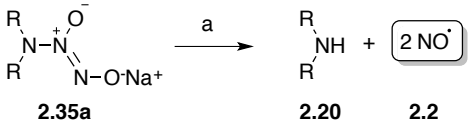
[45] J. F. DuMond, S. B. King, *Antioxid. Redox Signal.* **2011**, *14*, 1637.

[46] M. N. Hughes, P. E. Wimbledon, *J. Chem. Soc., Dalton Trans*., **1976**, 703.

[47] a) K. M. Miranda, A. S. Dutton, L. A. Ridnour, C. A. Foreman, E. Ford, N. Paolocci, T. Katori, C. G. Tocchetti, D. Mancardi, D. D. Thomas, M. G. Espey, K. N. Houk, J. M. Fukuto, D. A. Wink, *J. Am. Chem. Soc*. **2005**, *127*, 722; b) A. S. Dutton, J. M. Fukuto, K. N. Houk, *J. Am. Chem. Soc*. **2004**, *126*, 3795.

and at higher pH > 4, the N^1-oxygen surrounding is protonated and NO_2^- **2.14** and nitroxyl **2.12** is released. Nevertheless, further decomposition reactions indicating a complex mixture of several nitrogen-oxygen containing compounds are formed. Angeli's salt (**2.37**) is used as an NO^- **2.12** donor under physiological conditions and is used to promote vasodilation. However, the literature is inconsistent if $NO^\bullet$ **2.2** or NO^- **2.12** is responsible for vasorelaxation, due to different metabolic pathways of the applied NO-donors.[48,49]

N-diazeniumdiolates **2.35** are often referred as NONOates and are reported as the best NO-releasing functional group. The functional group is in general stable in the solid state as sodium adduct **2.35a** but hydrolyses in solution to $NO^\bullet$ **2.2** and amines **2.20** as shown in Scheme 2.5. The amount of released $NO^\bullet$ **2.2** can vary from one to two equivalents.[25,43]



2.35a **2.20** **2.2**

Scheme 2.5: Hydrolysis of *N*-diazeniumdiolates (**2.35**, NONOates). a) H_2O.

For this class of compounds not many synthetic methods are reported and the most used procedures are shown in Scheme 2.6a,[50] where an amine **2.20** is treated with gaseous $NO^\bullet$ **2.2** under basic conditions to form the sodium *N*-diazeniumdiolate **2.35a**. In the absence of an external base, the ammonium adduct **2.35b** is obtained (Scheme 2.6b). It was found that the sodium salts **2.35a** are more stable as their ammonium salts **2.35b**, which have the tendency to be hygroscopic. Zwitterionic diazeniumdiolate species **2.39** are formed by an additional intramolecular amine function **2.40** (Scheme 2.6c).

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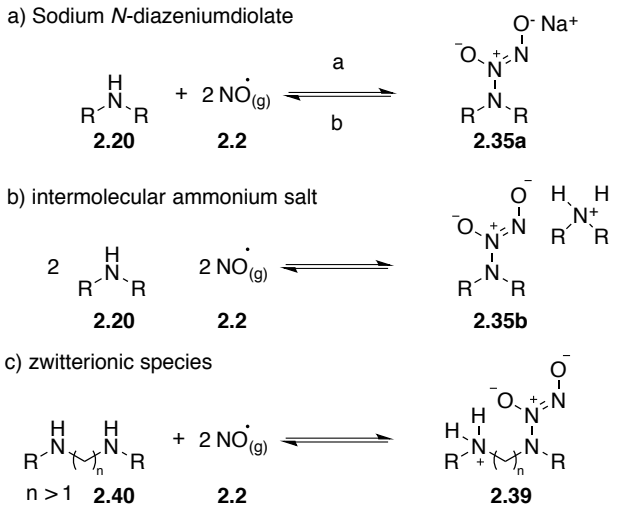
48 a) J. C. Wanstall, T. K. Jeffrey, A. Gambino, F. Lovren, C. R. Triggle, *Br. J. Pharmacol*. **2001**, *134*, 463; b) S. Nelli, Lorraine McIntosh, W. Martin, *Eur. J. Pharmacol.* **2001**, *412*, 281; c) Y. Shibata, H. Sato, I. Sagami, T. Shimizu, *Biochim. Biophys. Acta* **1997**, *1343*, 67; d) J. M. Fukuto, K. Chiang, R. Hszieh, P. Wong, G. Chaudhuri, *J. Pharmacol. Exp. Ther.* **1992**, *263*, 546.

49 R. Zamora, A. Grzesiok, H. Weber, M. Feelisch, *Biochem. J*. **1995**, *312*, 333.

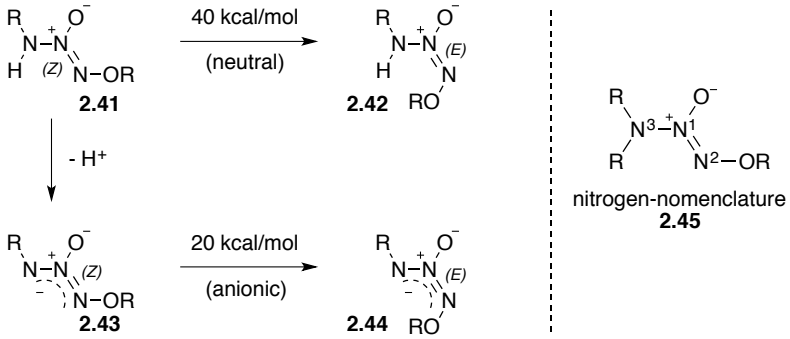
50 J. Konter, G. E.-D., A. A. Abou-Rahma, A. El-Emam, J. Lehmann, *Eur. J. Org. Chem*. **2007**, 616.



Scheme 2.6: Synthesis of NONOates.[50] a) NaOMe; b) H^+.

Mainly the *Z*-conformation **2.41** is either observed for diazeniumdiolates. The interconversion barrier to the *E*-diazeniumdiolate **2.42** was calculated for the neutral species to be around 40 kcal/mol. The strong N=N bond is restricted for a conformation change. The anionic *Z*-diazeniumdiolate **2.43** form showed a weaker bond energy of around 20 kcal/mol to the *E*-diazeniumdiolate **2.44**. The bond length of N^3-N^1 is 1.42 Å and of N^1-N^2 1.29 Å (nitrogen-nomenclature **2.45**, Scheme 2.7). The formation of the *E*-isomer was achieved by trapping the nucleophile with an installed electrophile on the O^2-mioety to form an intramolecular ring.[51]

[51] Y.-N. Wang, D. S. Bohle, C. L. Bonifant, G. N. Chmurny, J. R. Collins, K. M. Davies, J. Deschamps, J. L. Flippen-Anderson, L. K. Keefer, J. R. Klose, J. E. Saavedra, D. J. Waterhouse, J. Ivanic, *J. Am. Chem. Soc.* **2005**, *127*, 5388.



Scheme 2.7: Base promoted *E*/*Z*-isomerism of *N*-diazeniumdiolates **2.35**.

The formation of NONOates and their NO-releasing properties/stability strongly depends on the diazeniumdiolate structure. In general a slow NONOate formation corresponds to a slow NO-releaser. Steric and stereoelectronic effects influence the decomposition rate. More bulky substituents and incorporation of heteroatoms have an increasing effect on the NO-release properties. Cyclic substrates (**2.48** and **2.49**) accelerate the NO-release as shown in Figure 2.3.[50]

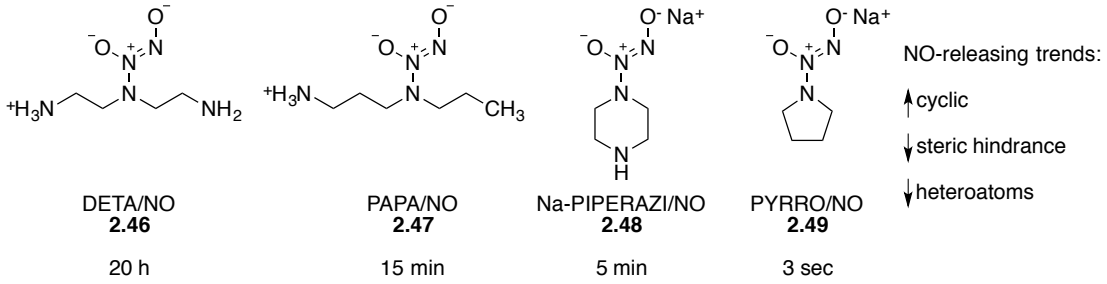


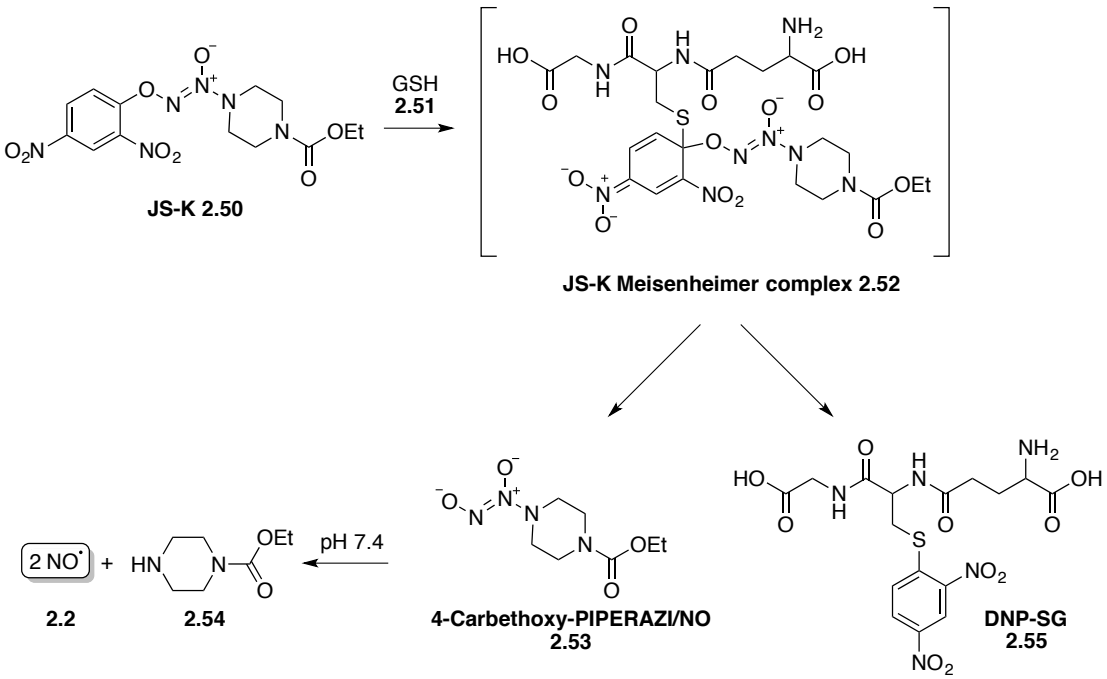
Figure 2.3: Half life time of various NO-releasers (NONOates).

So far, no *N*-diazeniumdiolate natural products have been found or reported, probably due to their instability towards physiological conditions. However, synthetic NONOate's are used for cancer treatment, but they showed in early studies severe side effects such as tissue damaging.[52] To increase the NONOate stability under physiological conditions, the O^2-substituent was modified to aryl-substituents. Furthermore, the stability under

[52] P. J. Shami, J. E. Saavedra, L. Y. Wang, C. L. Bonifant, B. A. Diwan, S. V. Singh, Y. Gu, S. D. Fox, G. S. Buzard, M. L. Citro, D. J. Waterhouse, K. M. Davies, X. Ji, L. K. Keefer, *Mol. Cancer Ther.* **2003**, *2*, 409.

physiological conditions can be increased by attaching the NONOate part to an ester moiety, which releases the NONOate part upon ester degradation by esterases.[53]

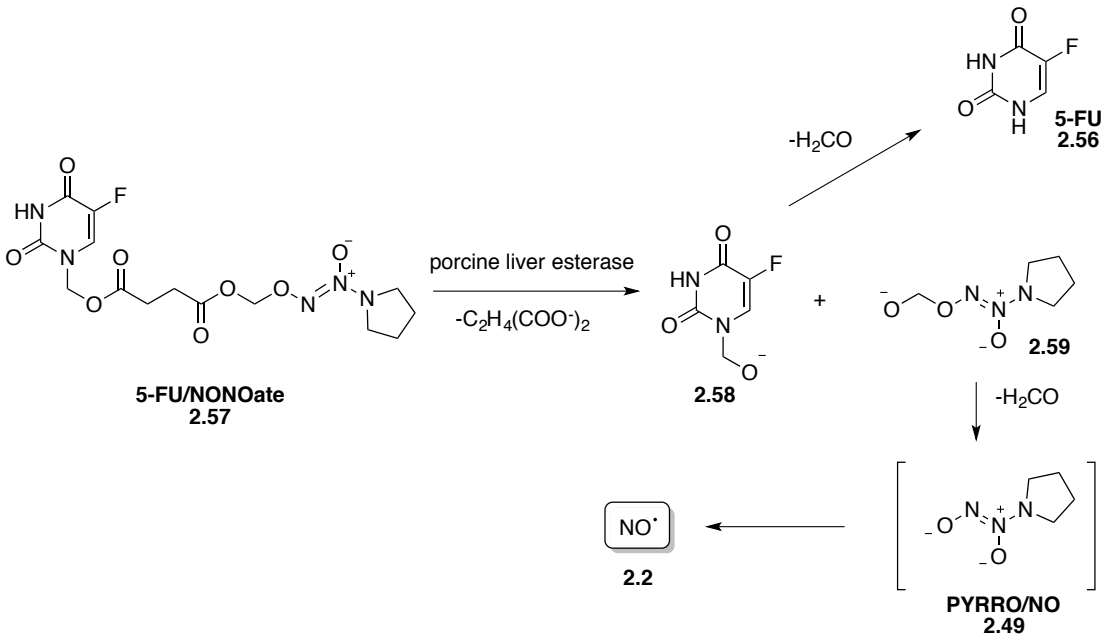
A promising anticancer candidate JS-K **2.50** possesses an IC_{50} value in the range of 0.2 – 0.5 μM in HL-60 (human myeloid leukemia) cell line.[52] The mode of action is illustrated in Scheme 2.8. First, JS-K **2.50** reacts with gluthathione (**2.51**, GSH) to form a Meisenheimer-complex **2.52**. The NONOate **2.53** is released, which further decomposes to the secondary amine **2.54** and NO$^{\bullet}$ **2.2**. The MAPK pathway (mitogen-activated protein kinase) is activated by NO$^{\bullet}$ **2.2**, which triggers cell apoptosis. Furthermore, DNP-SG **2.55** is formed, which has a supporting effect on cancer cell death or slower propagation.



Scheme 2.8: Biological mechanism of JS-K **2.50**.[52]

[53] J. E. Saavedra, P. J. Shami, L. Y. Wang, K. M. Davies, M. N. Booth, M. L. Citro, L. K. Keefer, *J. Med. Chem*. **2000**, *43*, 261.

5-Fluoroacyl (**2.56**, 5-FU) is used in the treatment of several cancer types. It represents an antimetabolite and possesses a similar structure as cytosin, thymin and uracil. It interacts with thymidylate-synthase and inhibits the cell division.[54] However, 5-FU **2.56** is less selective in tumor selection and other tissues are affected. Wang reported on an improved NONOate **2.57** derivate of 5-FU **2.56** with improved drug profile.[55] The NO-releasing mode is illustrated in Scheme 2.9. Porcine liver esterase cleaves the ester linker and the intermediates **2.58**, which degrades to 5-FU **2.56**, and **2.59** are formed. Latter decomposes to PYRRO/NO **2.49** and releases NO• **2.2**. 5-FU/NONOate **2.57** showed to be more active (65 mM in DU145 and 50 mM in HeLa cell) than 5-FU **2.56** (204 mM in DU145 and 278 mM in HeLa cell). It was claimed that a synergistic effect of NO• **2.2** and 5-FU **2.56** release increases the activity. However the safety profile was not evaluated.



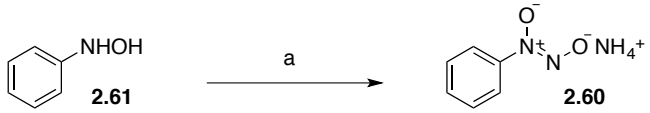
Scheme 2.9: Activation and NO-release mechanism of 5-FU/NONOate.[55]

[54] a) D. B. Longley, D. P. Harkin, P. G. Johnston, *Nat. Rev. Cancer* **2003**, *3*, 330; b) P. Noordhuis, U. Holwerda, C. L. Van der Wilt, C. J. Van Groeningen, K. Smid, S. Meijer, H. M. Pinedo, G. J. Peters, *Ann. Oncol.* **2004**, *15*, 1025.

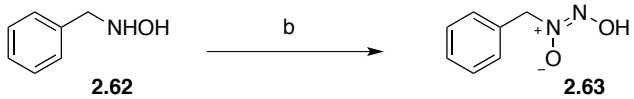
[55] T. B. Cai, X. Tang, J. Nagorski, P. G. Brauschweiger, P. G. Wang, *Bioorg. Med. Chem.* **2003**, *11*, 4971.

The most prominent *C*-diazeniumdiolate is cupferron (**2.60**), which is obtained *via* nitrosation of phenylhydroxylamine (**2.61**, Scheme 2.10a).[56] Due to the acidic lability of the functional group, basic conditions are normally applied and the products are obtained as their ammonium salts. The free acid can be obtained under acidic conditions with a mixture of $NaNO_2$ and HCl, as described by Behrend and König in their example of benzylhydroxylamine (**2.62**) to form the corresponding benzyl diazendiumdiolate **2.63** (Scheme 2.10b).[57] Addionally, an acidic work-up of the ammonium derivative will also yield in the free acid.

a) *C*-Diazeniumdiolate formation under basic conditions

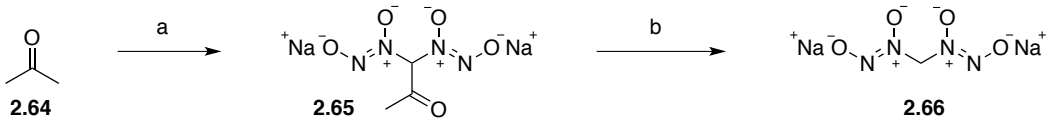


b) *C*-Diazeniumdiolate formation under acidic conditions



Scheme 2.10: Synthesis of *C*-diazeniumdiolates under different conditions. a) isopentyl nitrite, NH_3; b) $NaNO_2$, HCl.

Other methods include the use of enolates in a so called “Traube reaction” (Scheme 2.11).[58] Acetone (**2.64**) was treated under basic conditions with NO• **2.2** to form intermediate **2.65** and upon deacetylation, the bis-diazeniumdiolate sodium salt **2.66** was obtained.



Scheme 2.11: Traube reaction. a) NaOMe, nitric oxide (**2.2**); b) NaOMe.

As well as in the *N*-diazeniumdiolates **2.35**, also the *Z*-conformation **2.67** is predominantly present for *C*-diazeniumdiolates **2.36** (Figure 2.4a). This is

[56] C. S. Marvel, O. Kamm, *J. Am. Chem. Soc.* **1919**, *41,* 276.

[57] R. Behrend, E. Koenig, *Justus Liebigs Ann. Chem*. **1891**, *263*, 175.

[58] W. Traube, *Justus Liebigs Ann. Chem*. **1898**, *300*, 81.

presumably by the fact of hydrogen bonding properties of O^1-O^2 as well as steric interactions, which might results from a *E*-conformation.[59] Low temperature NMR-measurements were applied and a *E*/*Z*-conformation (**2.68** and **2.69**) change of around 15 kcal/mol was determined (Figure 2.4b).[60] However, for O^2-derivaties (H or acyclic/alkyl) no *E*-isomers have been reported yet.

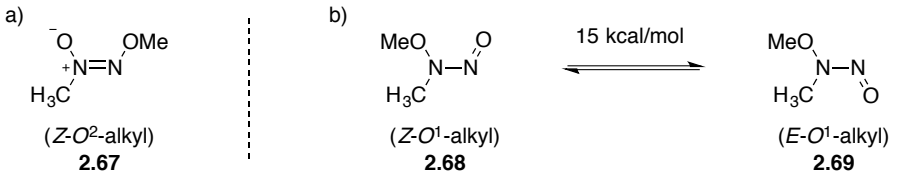


Figure 2.4: *E*/*Z*-interconversion of *C*-diazeniumdiolates.

Diazeniumdiolates are uncommon compounds and only a few of them have been isolated or reported. All of them are *C*-diazeniumdiolates. Figure 2.5 shows the most studied natural products and cupferron, which found applications in trace metal analysis.[61] Alanosine (**2.70**) is used as antitumor agent.[62] It is produced by the strain *Streptomyces alanosinicus*[63] and several syntheses[64] have been reported for this molecule including an impressive stereoselective six step synthesis with an overall yield of 49%.[65] Nitrosostromelin (**2.71**) was isolated from a *Streptomyces* culture and inhibits the protein stromelysin, which is proposed to be involved in tissue reconnection.[66] The metalloprotein has a zinc in the active center and useful applications were investigated in the treatment of rheumatoid arthritis and

[59] T. Axenrod, M. J. Wieder, G. W. A. Milne, *Tetrahedron Lett*. **1969**, *10*, 401.

[60] I. I. Chervin, S. S. Nasibov, V. F. Rudchenko, V. G. Shtamburg, R. G. Kostyanovskii, *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1981**, *30*, 544.

[61] N. H. Furman, W. B. Mason, J. S. Pecola, *Anal. Chem*. **1949**, *21*, 1325.

[62] a) A. K. Tyagi, D. C. Thake, E. Mcgee, D. A. Cooney, *Toxicology* **1981**, *21*, 56; b) J. Yu, *Curr. Opin. Investig. Drugs*. **2001**, *2*, 1623.

[63] Y. K. S. Murthy, J. E. Thiemann, C. Coronelli, P. Sensi, *Nature* **1966**, *211*, 1198.

[64] a) G. C. Lancini, A. Diena, E. Lazzari, *Tetrahedron Lett.* **1966**, *7*, 1769; b) Y. Isowa, H. Kurita, M. Ohmori, M. Sato, K. Mori, *Bull. Chem. Soc. Jpn*. **1973**, *46*, 1847.

[65] P. Strazzolini, M. G. Dall'Arche, M. Zossi, A. Pavsler, *Eur. J. Org. Chem*. **2004**, 4710.

[66] T. Umino, H. Yoshizaki, H. Wakatabe, *Chem. Abs*. **1996**, *125*, 245813.

osteoarthritis.[67] Dopastin (**2.72**) is another prominent antitumor candidate and inhibits β-dopamine-hydroxylase.[68] A total synthesis was reported in eight steps.[69]

Nitrosofungin (**2.73,** also sometimes referred as propanosine[70]) is an antifungal isolated from the bacterium *Alcaligenes*. Higher isolation yields were obtained when the bacterium was grown in mixed cultures with *Streptomyces plicatus*.[71] The authors proposed that a precursor is released from *Streptomyces* and incorporated into the synthesis of nitrosofungin (**2.73**) by *Alcaligenes*. A synthesis was reported by the same group starting from 2-nitro-1-propanol.[72]

Poecillanosine (**2.74**) has its origins from a marine sponge and therefore differs from other isolation sources.[73] It showed inhibition of lipid peroxidation of a rat brain homogenate (IC_{50} = 0.04 μM) and cytotoxicity against P388 murine leukemia cells (IC_{50} = 6.5 μM). Up to date only the O^1-methylated poecillanosine was synthesized.[74]

Cupferron (**2.60**) is not a natural product but found several applications in medicine (cupferron derivatives) and as metal-chelator, for the extraction of trace metal impurities in analytical chemistry.

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[67] S. Ye, P. Eriksson, A. Hamsten, M. Kurkinen, S. E. Humphries, A. M. Henney, *J. Biol. Chem*. **1996**, *271*, 13055.

[68] H. Iinuma, M. Matsuzaki, T. Nagatsu, T. Takeuchi, H. Umezawa, *Agr. Biol. Chem*. **1974**, *38*, 2107.

[69] H. Iinuma, N. Yagisawa, S. Shibahara, Y. Suhara, S. Kondo, K. Maeda, T. Takeuchi, M. Ohno, H. Umezawa, *Agric. Biol. Chem*. **1974**, *38*, 2099.

[70] Y. Abe, J.-I. Kadokura, A. Shimazu, H. Seto, N. Otake, *Agric. Biol. Chem*. **1983**, *47*, 2703.

[71] L. A. Dolak, T. M. Castle, B. R. Hannon, A. D. Argoudelis, F. Reusser, *J. Antibiot.* **1983**, *36*, 1425.

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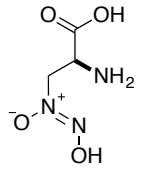
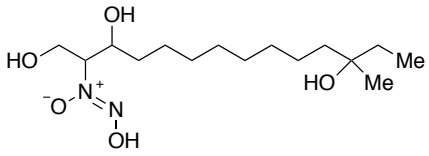
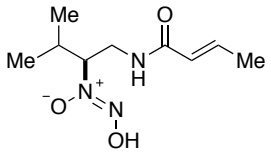
[74] M. Xian, B. J. Shuhler, *Tetrahedron Lett*. **2007**, *48*, 1209.



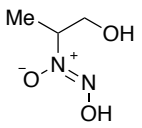
alanosine (**2.70**)



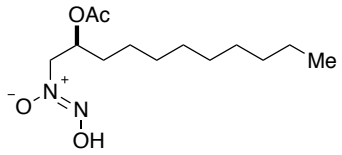
nitrososTromelin (**2.71**)



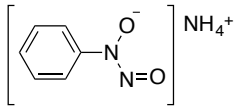
dopastin (**2.72**)



nitrosofungin (**2.73**)



poecillanosine (**2.74**)



cupferron (**2.60**)

Figure 2.5: *C*-Diazeniumdiolate containing molecules.

The biological formation of N=N bonds is still unclear and consists of a fundamental question in biological chemistry.[75] The source of the 2nd nitrogen source is still under debate. Possible sources[76] could be delivered *via* nitrogen fixation,[77] anammox pathway (**an**aerobic **amm**onium **ox**idation),[78] *via* the nitrate-nitrite-NO pathway[79] or delivered from other amino acids *via* degradation to HNO_2 **2.14a**.[80]

Most *C*-diazeniumdiolates are not able to act as a NO-donor, because they decompose to nitroxyl **2.12**, which reacts to N_2O **2.25** and the *C*-nitroso analogue. Installation of electron withdrawing group on the carbon moiety increases the changes for an NO-release, as shown for cupferron (**2.60**), a *C*-diazeniumdiolate, which can release $NO^{\bullet}$ **2.2** under thermal/photochemical conditions *via* an oxy-radical species **2.75** and further decomposition to nitrosobenzene **2.76** (Scheme 2.12).[81]

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[79] J. O. Lundberg, E. Weitzberg, M. T. Gladwin, *Nat. Rev. Drug Discov.* **2008**, *7*, 156.

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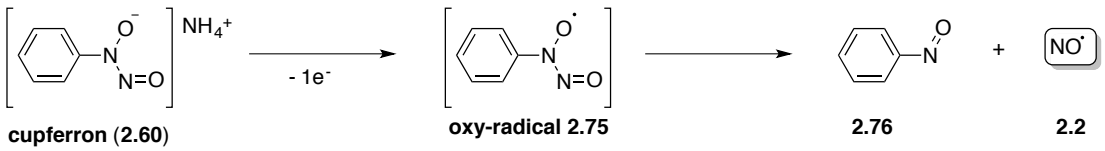
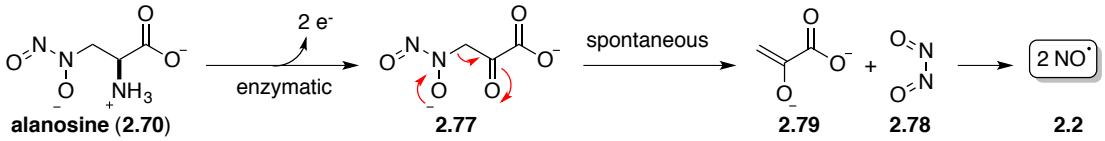
[81] J. R. Hwu, C. S. Yau, S.-C. Tsay, T.-I. Ho, *Tetrahedron Lett.* **1997**, *38*, 9001.



Scheme 2.12: Generation of NO• **2.2** from cupferron (**2.60**) *via* 1e⁻ reduction.

Nevertheless, NO-releasing of *C*-diazeniumdiolates are known and follows an enzymatic induced degradation process as shown in Scheme 2.13 for the NO-release of alanosine (**2.70**).[82] A transamination forms a α-ketoacid **2.77** intermediate, which releases N_2O_2 **2.78** and an enol **2.79**. N_2O_2 **2.78** is the dimeric form of NO• **2.2**.



Scheme 2.13: Enzymatic degradation of alanosine (**2.70**).

In the laboratory, NO-gas can be synthesized by treating $FeSO_4$ with $NaNO_2$ under acidic conditions.[83]

Metal-chelators are playing an important role in biological system,[84] especially siderophores,[85] which are binding to Fe. As aforementioned, *C*-diazeniumdiolates **2.36** are less known for NO-release, but can act as metal-chelator especially to form copper-complexes.[86] Chelating studies on the anticancer drug alanosine (**2.70**) showed a strong chelating effect on Cu^{II} with comparable binding affinities as EDTA.[87] Furthermore, dopastin (**2.72**) is a potent inhibitor of the copper-dependent dopamine β-hydroxylase.[69]

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83 M. G. Suryaraman, A. Viswanathan, *J. Chem. Educ*. **1949**, *26*, 594.

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2.2 Goal of this Study and Synthetic and Biosynthetic Investigations of Fragin

In collaboration with the group of Prof. Dr. Leo Eberl and his student Christian Jenul, my colleague Dr. Simon Sieber from the Gademann group isolated the natural product fragin (**2.80**) from a *Burkholderia cenocepacia* sample (Figure 2.6).[88] Interested by the potential biological activity of this compound and the mode of action, we elaborated a biological and synthetic program. Furthermore, the stereocenter of fragin (**2.80**) remained unknown and we started a synthetic program to synthesize fragin (**2.80**) in an enantioselective fashion. Additionally, further biological activity profile and biosynthetic pathway elucidation were studied in this chapter.

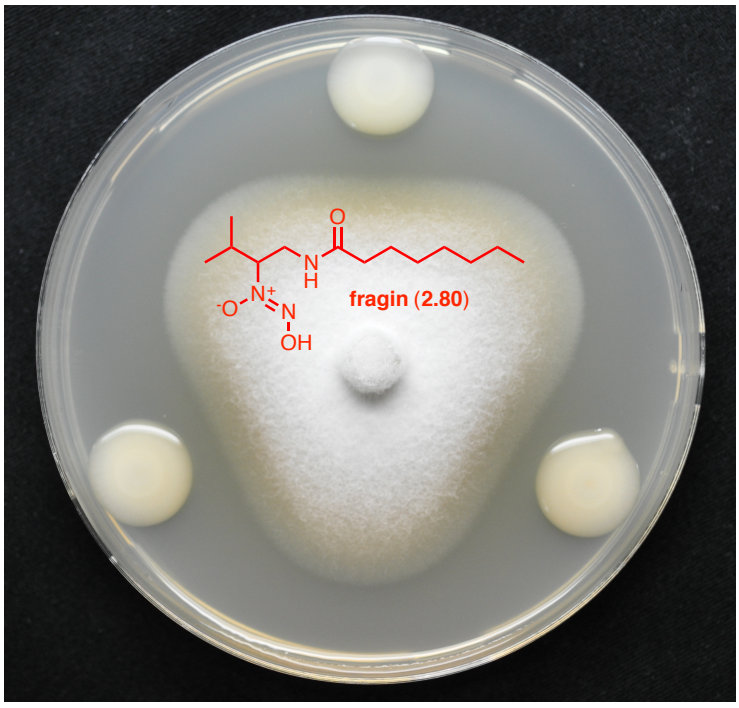

Figure 2.6: Antifungal activity of fragin (**2.80**) against *Burkholderia cenocepacia*. Picture of the plate provided by Christian Jenul (University of Zurich).

[88] S. Sieber, Ph. D. Thesis, *„Addressing Fundamental Questions in Chemical Biology trough Biochemical Investigations of Natural Products“*, University of Basel **2015**.

2.2.1 Tamura's Total Synthesis of (±)-Fragin

The natural product fragin (**2.80**) was first described by Tamura and co-workers in 1967.[89] It was isolated from *Pseudomonas fragi* and showed inhibiting activities against lettuce seedlings, *Aspergillus niger* and chlorella.[90] In the same year, a first racemic total synthesis of fragin (**2.80**) was published by the Tamura group (Scheme 2.14).[91] Starting from isobutyryl chloride (**2.81**), a Nierenstein reaction afforded chloromethyl ketone **2.82**. A Gabriel synthesis furnished first the desired amide intermediate **2.83**, which was cleaved under acidic conditions to the ammonium salt intermediate **2.84**. Treating the salt **2.84** with octanoyl chloride afforded the fatty acid product **2.85** in 73%. The same key intermediate **2.85** was synthesized in a second synthesis starting from isobutyryl aldehyde (**2.86**), which was treated under basic conditions in nitromethane (Henry-reaction) to afford the nitroalcohol **2.87**. The nitro group was hydrogenated to the corresponding free amine **2.88**, which was treated with octanoyl chloride to the fatty acid product **2.89**. The alcohol **2.89** was then oxidized using Jones' reagent to the common ketone intermediate **2.85** in 75% yield. The oxime **2.90** was synthesized in the presence of hydroxylamine hydrochloride and NaOAc in 85%. Reducing attempts to the hydroxylamine **2.91** with diborane were not successful due to the coordinating effect of the adjacent amide function. Finally, a catalytic hydrogenation over Pt/C furnished the hydroxylamine **2.91** in a good yield of 70%. The final racemic natural product fragin (**2.80**) was achieved by treating the hydroxylamine **2.81** with $NaNO_2$ under aqueous acidic conditions and (±)-fragin (**2.80**) was isolated as a white solid in 83% yield (eight steps, 23%).

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89 S. Tamura, A. Murayama, K. Hata, *Agr. Biol. Chem*. **1967**, *31*, 758.

90 A. Murayama, K. Hata, S. Tamura, *Agr. Biol. Chem*. **1969**, *33*, 1599.

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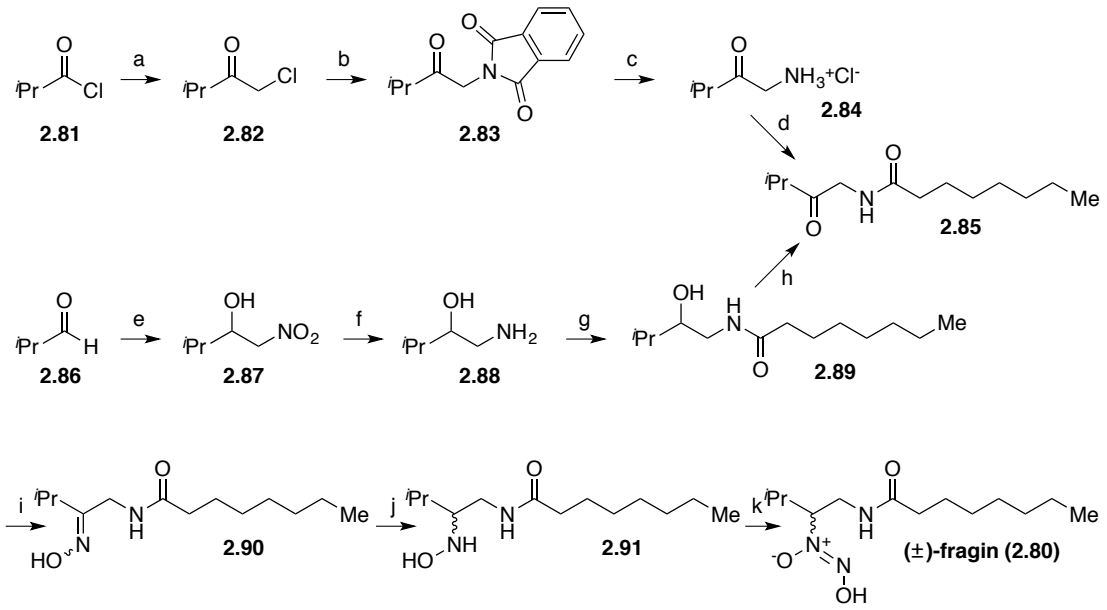
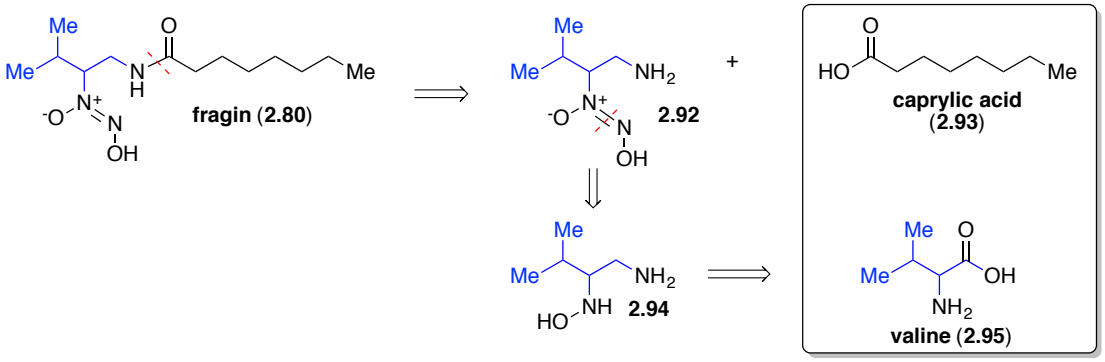


Scheme 2.14: Tamura's total synthesis of (±)-fragin (**2.80**). a) diazomethane, $HCl_{(g)}$; b) potassium phthalimide, DMF; c) HCl, 63% (over three steps); d) octanoyl chloride, NaOH, 73%; e) nitromethane, NaOH; f) Raney-Ni, H_2, 62% (over two steps); g) octanoyl chloride, NaOH, 90%; h) Jones' reagent, acetone, 75%; i) hydroxylamine hydrochloride, NaOAc, 85%; j) Pt/C, H_2, MeOH, HCl, 70%; k) $NaNO_2$, HCl, 83%.

2.2.2 Retrosynthetic Analysis and Enantioselective Total Synthesis of (–)-Fragin

The stereocenter of the naturally isolated fragin (**2.80**) remained unknown and thereof, we decided to elaborate an enantioselective synthesis of fragin (**2.80**). A retrosynthetic analysis revealed that the molecule can be divided in an amine **2.92** and a fatty acid part (caprylic acid (**2.93**)) as shown in Scheme 2.15. The installation of the diazeniumdiolate group will be done in the last step of the synthesis from a hydroxylamine intermediate **2.94**, which is derived from the amino acid valine (**2.95**).



Scheme 2.15: Retrosynthetic analysis of fragin (**2.80**).

The synthesis starts from enantiopure Fmoc-protected valine (**2.96a** and **2.96b**), which is commercially available in the respective enantiopure form (Scheme 2.16). The carboxylic acid **2.96a** and **2.96b** was reduced to the alcohol **2.97a** and **2.97b** in a one pot procedure according to Liskamp and co-workers (Scheme 2.16).[92] A modified Mitsunobu reaction furnished the azide **2.98a** and **2.98b**. The reported reduction using Pd/C and H_2 could only be reproduced in a moderate yield of around 50%. It is known that the Fmoc-moiety could be sensitive under this condition and a milder reducing condition was found using Pd/C and triethylsilane as the H_2-donor.[93] The ammonium salt **2.99a** and **2.99b** could be filtrated and washed with pentane (to remove silane by-products) to yield the desired ammonium salt **2.99a** in an excellent and reproducible yield of 87% and a moderate yield of 56% for ammonium salt **2.99b** under the reported hydrogenation conditions. The fatty acid chain part was introduced with octanoyl chloride to yield the amide **2.100a** and **2.100b** in moderate to excellent yields. The Fmoc-cleavage was found to be challenging. Under standard deprotection conditions with amine bases (piperidine, DBU) only small amounts of the free amine **2.101a** and **2.101b** could be isolated. Furthermore, the excess of base and the formed dibenzofulvene-adduct as a byproduct made the work-up as well as purification much more complicated. A base free Fmoc-deprotection condition using $AlCl_3$ as Lewis-acid was conducted and a simple acidic and basic work-up yielded the free amine **2.101a** and **2.101b** in a remarkable yield of 95%

[92] A. Boeijen, J. van Ameijde, R. M. J. Liskamp, *J. Org. Chem.* **2001**, *66*, 8454.

[93] P. K. Mandal, J. S. McMurray, *J. Org. Chem.* **2007**, *72*, 6599.

and 92%.[94] The mechanism is unknown, but we are suggesting that the Lewis-acid binds to the carbonyl function and the released chloride is abstracting the hydrogen in a $E1_{cb}$–fashion to form dibenzofulvene and CO_2 as the sole byproduct. Oxidation of amines to hydroxylamines[95] or even nitro-functionalities[96] are rarely described in literature. Classical approaches for the conversion of amines to hydroxylamines involve a condensation of a benzaldehyde moiety followed by an oxaziridation of the formed imine, which is then cleaved under acidic conditions to the hydroxylamine.[69] However, hydroxylamines are not very stable and can be oxidized to the undesired oxime. An alternative two step procedure was used in this case. The amine reacted with dibenzoylperoxide to the *N*-oxidized intermediate **2.102a** and **2.102b**, however traces of the amide product was observed as a minor product.[97] The cleavage of the benzoyl-group was achieved with hydrazine and the hydroxylamine **2.91a** and **2.91b** could be isolated with an acidic and basic work-up in a moderate (Scheme 2.16). We suggest the instability during the reaction and work-up process is responsible for this moderate yield. The final step was already reported by the Tamura group, using $NaNO_2$ in acidic aqueous medium.[91] To our surprise, several attempts failed, even with multiple additions of $NaNO_2$ into the acidic solution. We were pleased that the missing NO-functionality could be introduced by isopentyl nitrite as the NO-donor under basic conditions. A simple basic and acidic work-up furnished the desired natural product (–)-fragin (**2.80a**) and (+)-fragin (**2.80b**) as a white solid in a yield of 83%. The structure of (–)-fragin (**2.80a**) was secured by X-ray crystal structure analysis. Overall, the enantioselective total synthesis (–)-fragin (**2.80a**) was achieved in eight steps with an overall yield of 13%.

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94 A. Leggio, A. Liguori, A. Napoli, C. Siciliano, G. Sindona, *Eur. J. Org. Chem*. **2000**, 573.

95 J. Hu, M. J. Miller, *J. Am. Chem. Soc.* **1997**, *119,* 3462.

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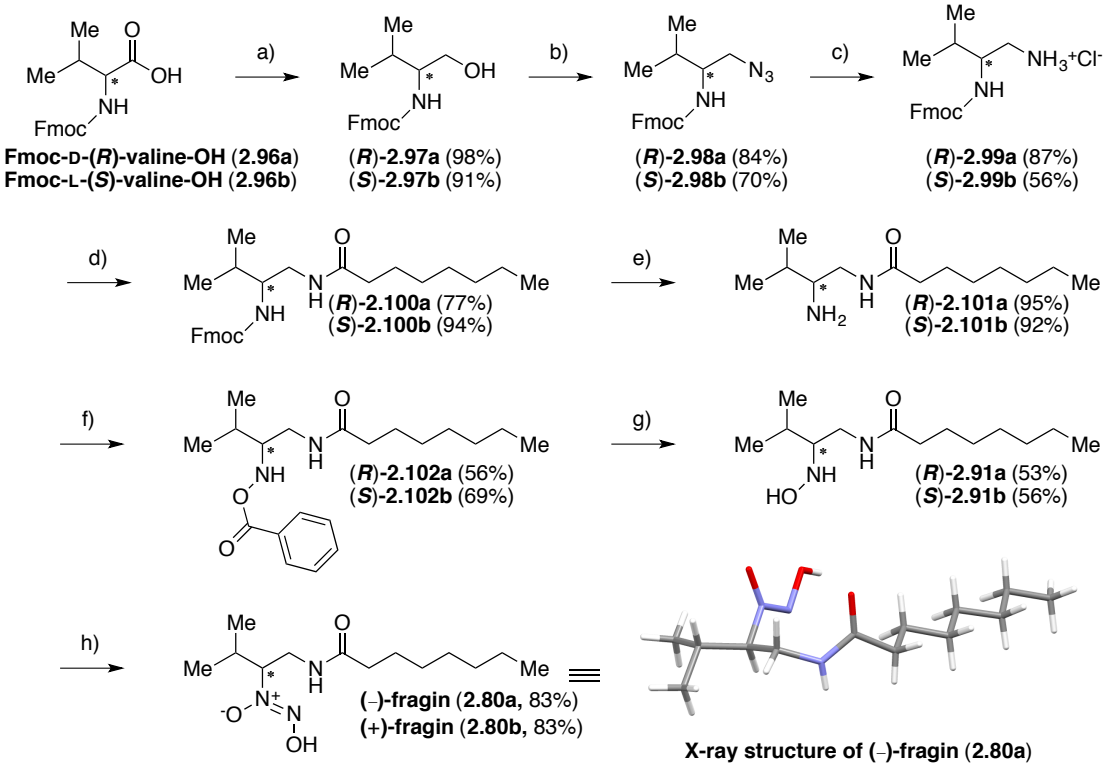
97 Z.-Y. Chang, R. M. Coates, *J. Org. Chem*. **1990**, *55*, 3475.



Scheme 2.16: Enantioselective total synthesis and X-ray structure of (–)-fragin (**2.80a**) and (+)-fragin (**2.80b**), X-ray structure color code: blue = nitrogen; grey = carbon; red = oxygen; white = hydrogen. a) Isobutylchloroformiate, $NaBH_4$, DME, r.t. 1.5 h; b) PPh_3, DEAD, DPPA, THF, 0 °C – r.t., 10 h; c) Pd/C, Et_3SiH, MeOH/$CHCl_3$, 14 h, r.t.; d) octanoyl chloride, DIPEA, DMAP, 14 h, r.t.; e) $AlCl_3$, toluene, 3.5 h, r.t.; f) dibenzoylperoxide, K_2HPO_4, THF, 21 h, r.t.; g) N_2H_4 x H_2O, EtOH, 2.5 h, r.t.; h) isopentyl nitrite, $NH_{3(g)}$, EtOH, 0.5 h, r.t.

The ^{1}H- and ^{13}C-NMR spectra were in good agreement with the isolated natural product as depicted in Figure 2.7. Both synthesized fragin enantiomers (**2.80a** and **2.80b**) were compared with the optical rotation of the published molecule as well as the newly isolated fragin (**2.80**) in our group.[88] The stereocenter was finally assigned as (*R*)-configured (–)-fragin **2.80a**. This was furthermore confirmed by X-ray crystal structure analysis of the isolated and synthesized sample.

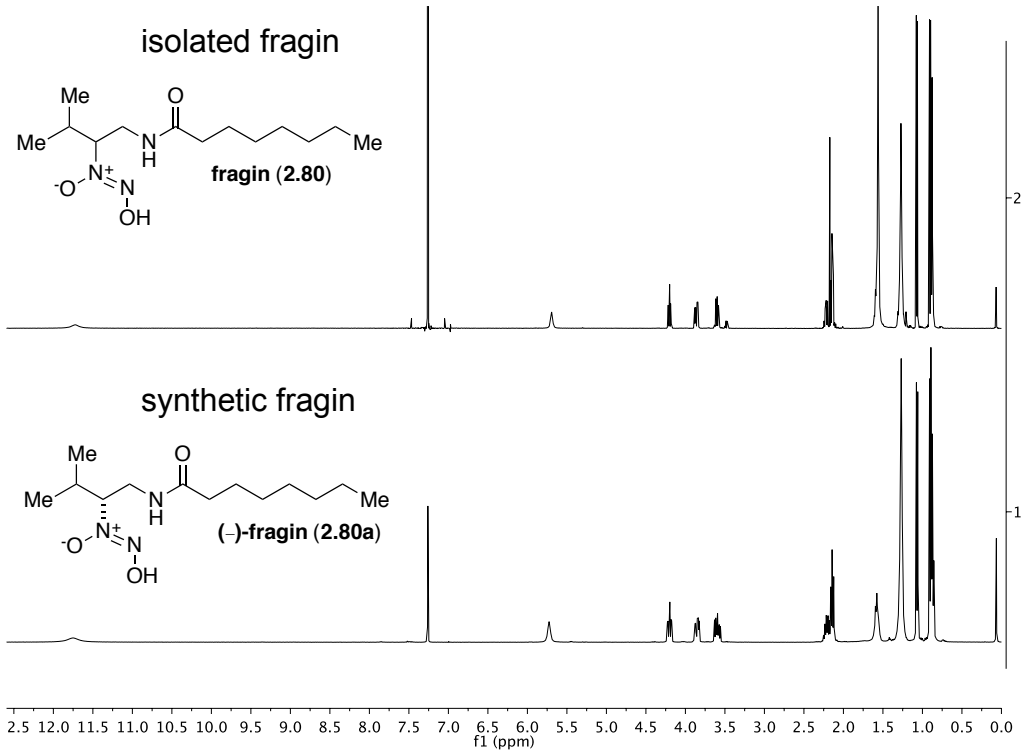
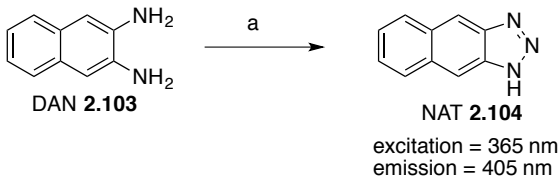


Figure 2.7: ^{1}H-NMR spectra of isolated fragin (**2.80**, top) and synthetic (–)-fragin (**2.80a**, bottom) (400 NMR, $CDCl_3$).

2.2.3 NO-Releasing Measurements of (–)-Fragin

The degradation studies of Tamura and co-worker showed that an acetic acid treatment of fragin (**2.80**) formed the nitrosodimer.[89] However, the two missing NO-parts were not further described. We assume that a release of NO• **2.2** might happen. To test this assumption, we followed a NO-detection procedure using 2,3-diaminonaphtalene (DAN, **2.103**), which acts as a NO-scavenger and forms the fluorescent 1-[H]-naphthotriazole (NAT, **2.104**) as shown in Scheme 2.17.[98]



Scheme 2.17: NO-detection by scavenging NO• **2.2** and measuring of the fluorescent NAT **2.104**. a) NO•

[98] M.-C. Carré, B. Mathieuxe, J.-C. André, M.-L. Viriot, *Analusis* **1999**, *27*, 835.

A mixture of (−)-fragin (**2.80a**) in $CHCl_3$/AcOH and DAN (**2.103**) was measured. The expected peak at 405 nm was observed and a NO-release could be confirmed after 1 h and 5 h (representative spectra shown in Figure 2.8). The emission spectra after 24 h showed a different spectra, probably due to degradation of DAN (**2.103**) or the resulting product. The quenched samples were analyzed by HPLC to quantify the NO-release. However, all the samples (time range from 1 h, 5 h and 24 h) showed no significant change in the (−)-fragin (**2.80a**) concentration as well no expected other products were detected. We could not reproduce the expected degradation of (−)-fragin (**2.80a**) as described by Tamura in our testing method.[89] The DAN test is very sensitive and already minor amount of NO-release can be observed.

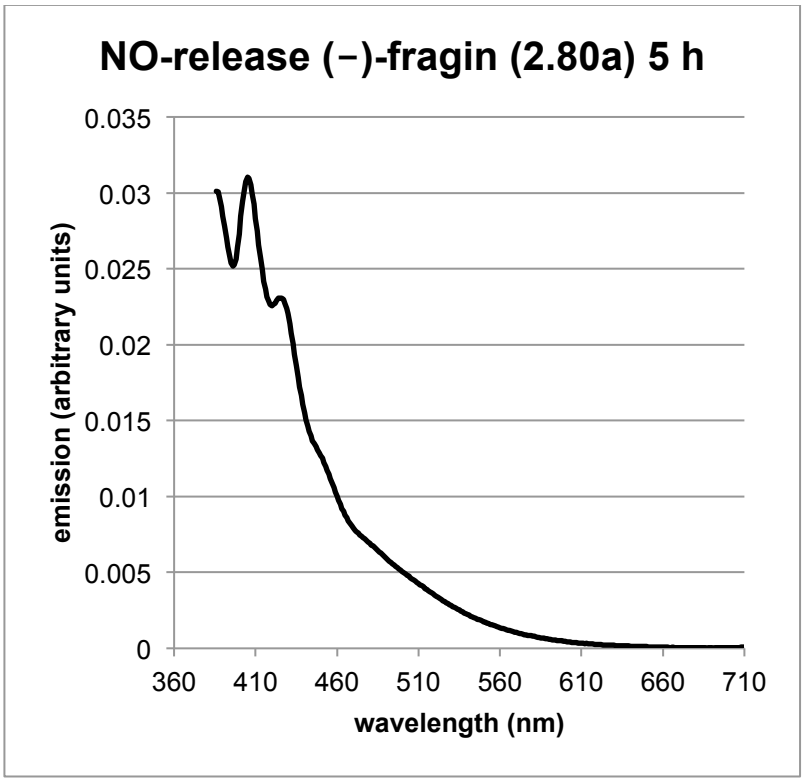


Figure 2.8: UV-VIS spectra of quenched fragin-DAN-solution after 5 h.

To conclude, the data suggest that (−)-fragin (**2.80a**) can act as a slow NO-releaser, but other quantification methods should be tested for further evidence. Additionally, physiological conditions should be tested for possible *in vivo* NO-release properties.

2.3 Isolation and Enantioselective Synthesis of the Signaling Molecule Valdiazen

In the studies of the natural product (–)-fragin (**2.80a**), our collaborator Christian Jenul (University of Zurich) observed a signaling molecule **2.105**, which regulates the ham-gene cluster and is suspected also to be an intermediate in the biosynthesis of (–)-fragin (**2.80a**). Encouraged by these findings, we focused on the isolation of this intermediate from the strain *Burkholderia cenocepacia H111*. The identification was achieved as described. First, gene sequence was identified. Secondly, the molecule **2.105** was isolated by extraction, isolated by HPLC and analyzed by NMR, mass spectrometry and X-ray structure analysis. Based on this result a signaling molecule structure **2.105** was proposed. Thirdly, a synthesis confirmed the structural proposal. The general work-flow Scheme is highlighted in Figure 2.9.

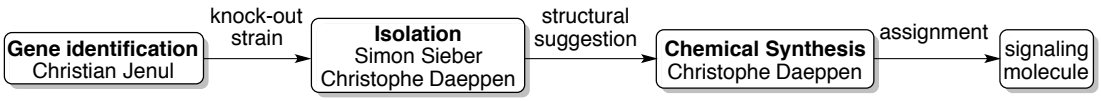


Figure 2.9: Identification of the natural product valdiazen.

A method to follow a biosynthetic pathway of a natural product is the identification of the gene-sequence and then the preparation of the knock-out strains. (The functions of the genes are discussed in detail in the biosynthetic investigation chapter 2.4.3). The knock-out strains of the ham-gene cluster were prepared by Christian Jenul from the group of Prof. Dr. Leo Eberl. Out of this gene, the knock-out strain hamF was found to produce the signaling molecule **2.105** in a suitable amount for further studies. The gene-analysis revealed that the signaling molecule should also consists of the diazeniumdiolate functional group and the extraction of the hamF supernatant was performed *via* a basic and acidic work-up (see experimental part for a detailed procedure). The extracts were purified by HPLC using a Synergi Hydro column (see experimental part for further details). The signaling molecule HPLC isolation trace is shown below (Figure 2.10)

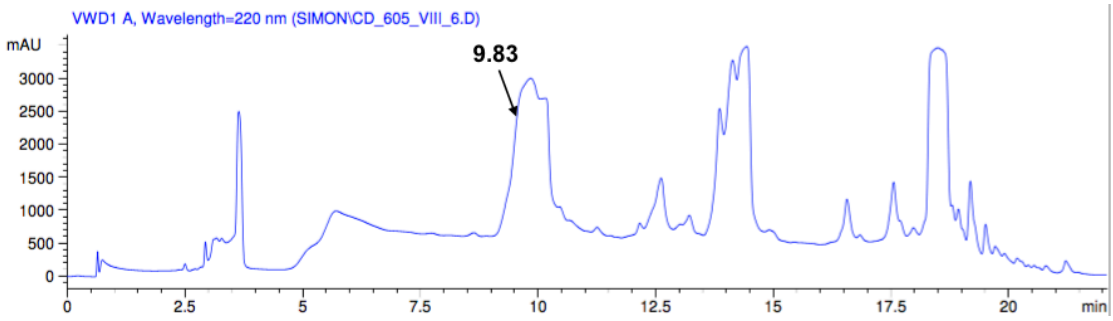


Figure 2.10: HPLC-trace of the signaling molecule **2.105** (9.83 minutes) sample after extraction.

The isolated fractions were tested on their biological activity for the signaling molecule **2.105** (9.83 min, Figure 2.10) activity by Christian Jenul. The active fractions were then further analyzed. A first NMR-analysis of a crude sample showed that the molecule consists of an isopropyl function and protons at 4.0 ppm (two protons) and 3.8 ppm (one proton). HSQC-analysis indicated the same carbon correlation of the one proton at 4.0 ppm and the signal at 3.8 ppm. The structure of **2.105** was further compared with the ^{1}H-NMR data of fragin (**2.80**).[88] The fatty acid moiety is not present in the novel structure **2.105**. The CH_2-shifts (4.0 and 3.8 ppm) are too high for a free amine, therefore a free alcohol moiety was proposed. Based on the similar ^{1}H-NMR spectra of fragin (**2.80**) and the novel structure **2.105** as well as the basic and acidic extractive work up, a diazeniumdiolate group for the novel structure **2.105** was proposed. Furthermore, the shift for the second proton at 4.0 ppm is in good agreement with the proton shift of fragin (**2.80**), containing a diazeniumdiolate function adjacent to this proton. Out of these structural findings, a first structural suggestion for the signaling molecule **2.105** was done and summarized in Figure 2.11.

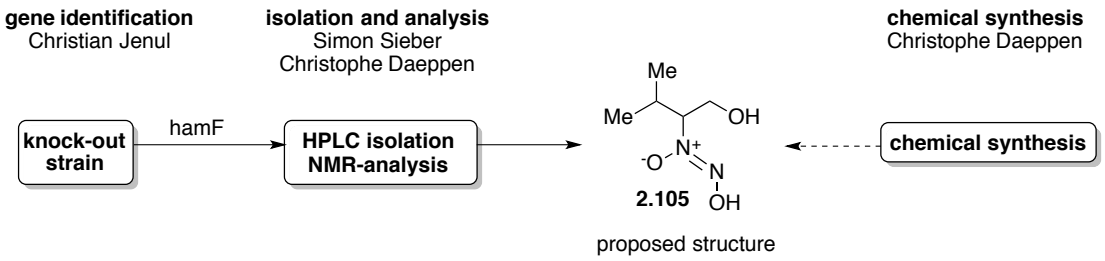
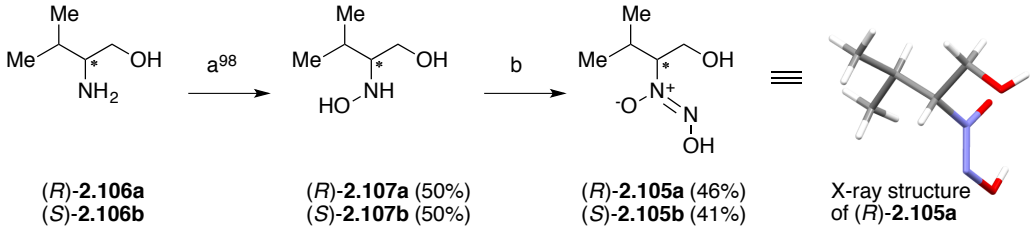


Figure 2.11: Structure elucidation pathways of the proposed signaling molecule structure **2.105**.

The enantioselective total synthesis for both enantiomers of the signaling molecule **2.105** are depicted in Scheme 2.18. Commercial available and enantiopure valinol (**2.106a** and **2.106b**) was used and condensated with *para*-methoxybenzaldehyde. An oxaziridation of the formed imine and further opening of the oxaziridine intermediate with hydroxylaminehydrochloride furnished the desired hydroxylamines **2.107a** and **2.107b** which was used without further purification.[99] The hydroxylamines **2.107a** and **2.107b** were treated with isopentyl nitrite under basic conditions and the desired signaling molecules (–)-**2.105a** and (+)-**2.105b** could be isolated by a simple basic and acidic work-up. The structure was additionally secured by X-ray crystal structure analysis (Scheme 2.18). Due to its similarity to fragin (**2.80**) and valinol (**2.106**), the compound was named valdiazen (**2.105**).



Scheme 2.18: Total synthesis of both enantiomers of the signaling molecule **2.105** and X-ray structure of (*R*)-valdiazen **2.105a** (X-ray structure color code: blue = nitrogen; grey = carbon; red = oxygen; white = hydrogen). a) PMP-CHO, CH_2Cl_2, r.t., 4 h, then *m*-CPBA, CH_2Cl_2, 0 °C to r.t., 2 h, then NH_2OH x HCl, MeOH, r.t., 3 d; b) isopentyl nitrite, NH_3 in MeOH, r.t., 45 min.

The ^{1}H-NMR (Figure 2.12) as well as the ^{13}C-NMR (Figure 2.13) of isolated and synthetic valdiazen (**2.105**) are in good agreement with the synthetic onces. Small changes might arise from the acidic properties of the diazeniumdiolate function.

[99] M. Breuning, T. Häuser, E-.M. Tanzer, *Org. Lett*. **2009**, *11*, 4032.

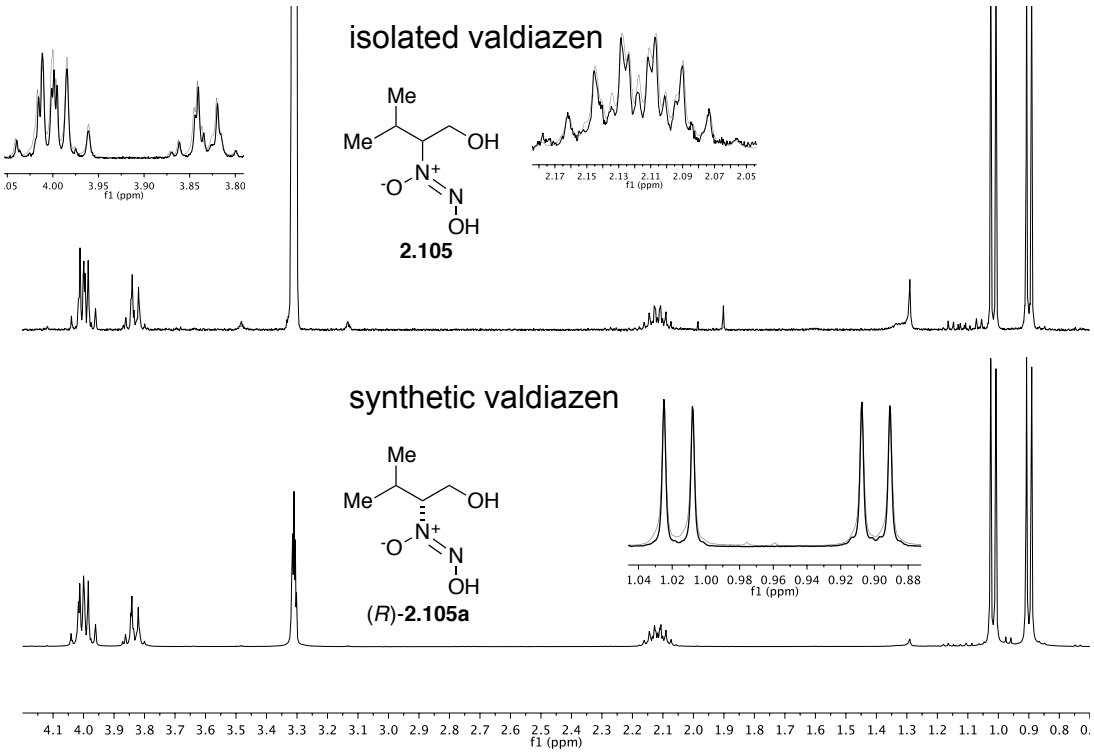


Figure 2.12: ^{1}H-NMR spectra of isolated **2.105** (top) and synthetic (–)-valdiazen (**2.105a**) (bottom) and peak overlays (600 NMR, MeOD).

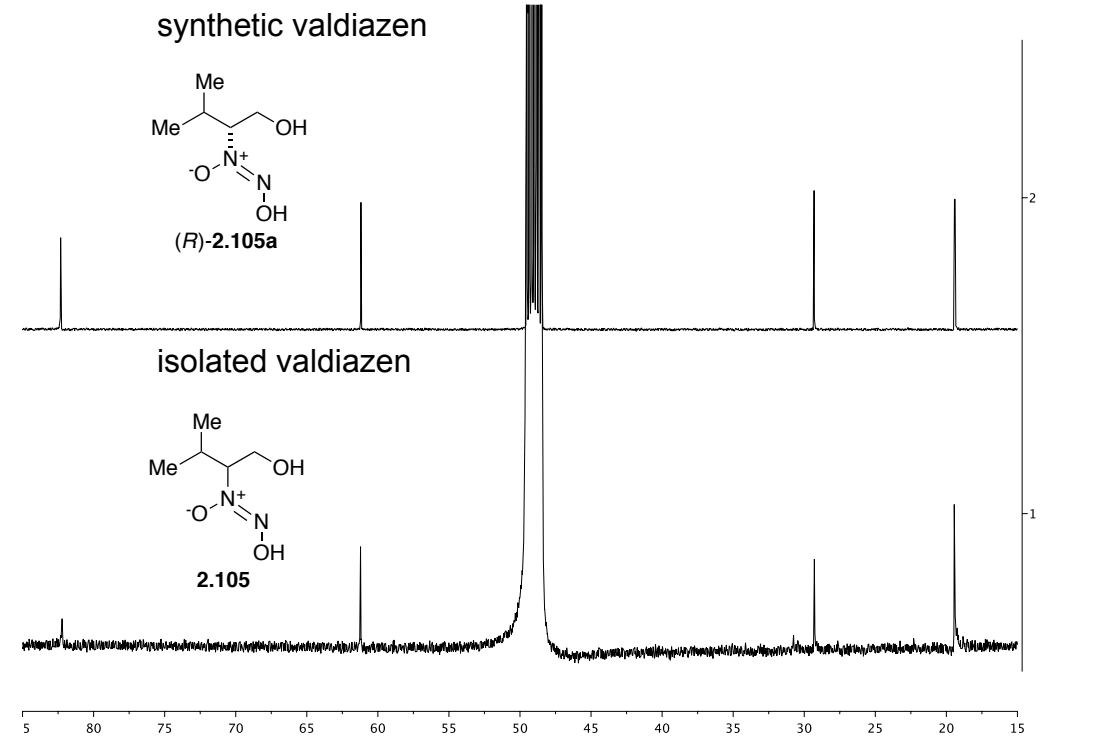
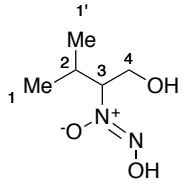


Figure 2.13: ^{13}C-spectra of synthetic (–)-**2.105a** (top) and isolated valdiazen (**2.105**) (500 NMR, MeOD).

The NMR data for valdiazen (**2.105**) are concluded in Table 2.1.



valdiazen (**2.105**)

atom Nr.	$^{1}H^{a}$	$^{13}C^{a}$	COSY	HMBC
1	1.02 (d, *J* = 6.8 Hz)	19.4; CH_3	2	1', 2, 3
1'	0.90 (d, *J* = 6.8 Hz)			1, 2, 3
2	2.12 (m)	29.3; CH	1/1', 3	1/1', 3
3	4.00 (m)	82.3; CH	2	4
4	4.00 (m)	61.2; CH_2	3, 4'	2, 3
4'	3.83 (m)	-	3, 4	-
OH	-	-	-	-
N-OH	-	-	-	-

Table 2.1: ^{1}H- and ^{13}C-NMR analysis of valdiazen (**2.105**) in MeOD. ^{a} (δ/ppm; signal)

Due to the low amount from the isolation (0.5 – 1 mg), the stereocenter of isolated valdiazen (**2.105**) could not be unambiguously confirmed by optical rotation value and other methods were considered. Chiral GC was performed but the product could not be detected. However GC-analysis showed several fragments, which would correspond to a NO-released hydroxylamine fragment (mass = 88.0; EI-fragmentation). The same mass fragment spectrum was observed by injecting the pure hydroxylamine **2.107a**. The isolation was performed by HPLC-separation and suitable conditions were found for chiral HPLC analysis. The racemate was prepared by mixing an equimolar amount of the synthetic enantiomers (–)-**2.105a** and (+)-**2.105b**. Additional both single enantiomers of synthetic valdiazen ((–)-**2.105a** and (+)-**2.105b**) were injected and finally the isolated valdiazen (**2.105**) as shown in Figure 2.14. The racemate could be separated and both enantiomers are stable under the used conditions and no racemization occurs. To our surprise, the isolated valdiazen (**2.105**) is racemic as shown in Figure 2.14. This observation is in detailed discussed in the biosynthesis section of this thesis (see chapter 2.4.3).

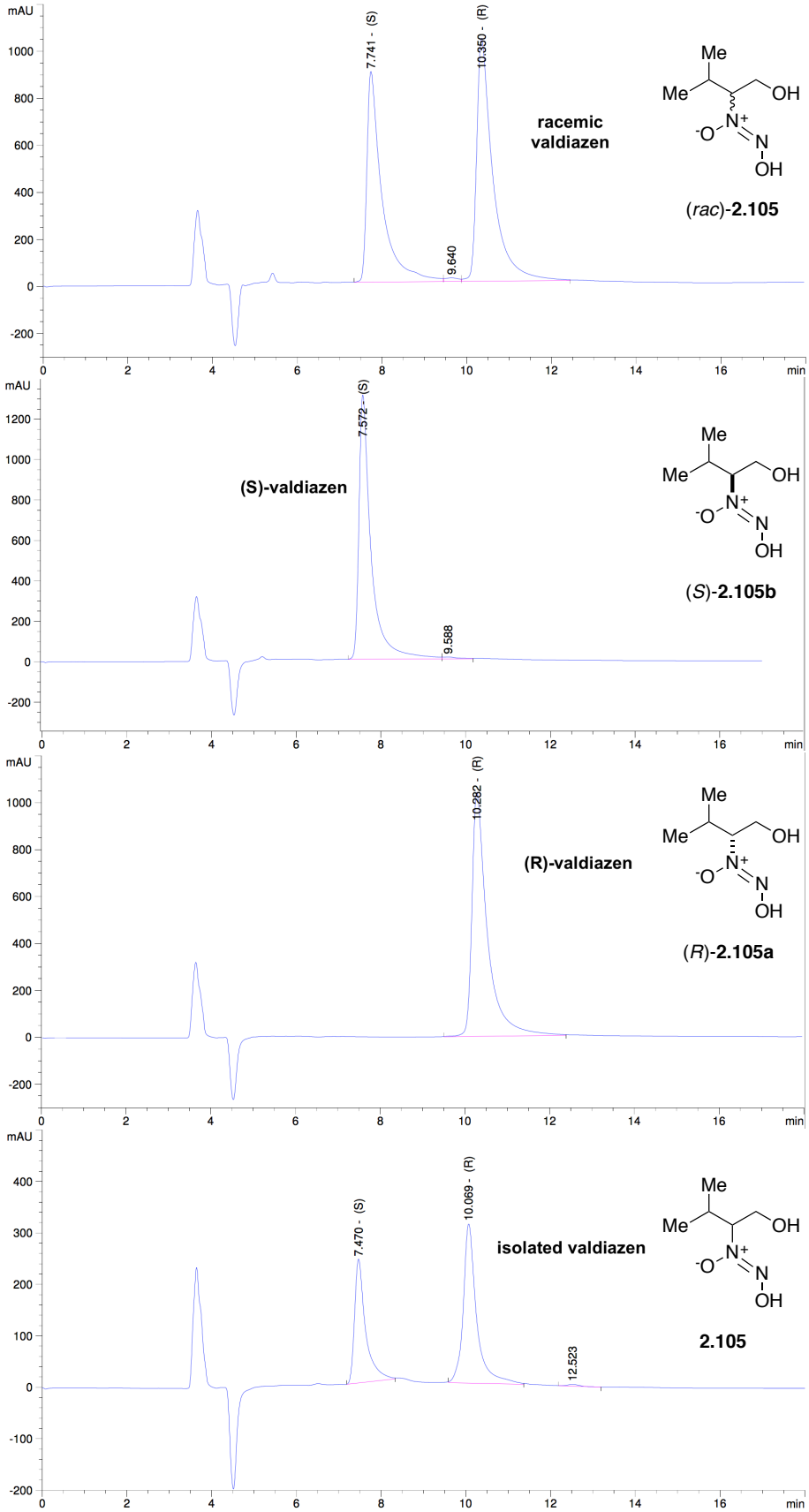


Figure 2.14: Chiral HPLC analysis of synthetic (*R*)-**2.105a** and (*S*)-valdiazen (**2.105b**), racemate (*rac*)-**2.105**) and isolated valdiazen (**2.105**).

The pKa of synthetic (–)-valdiazen (**2.105a**) was measured by Jrène Lehmann (Mass Spectrometry Service at the University of Zurich). It showed a pKa of 5.5 (see experimental part of this thesis), which is in good agreement with previously reported pKa-values for diazeniumolates.[69,100]

To conclude, an intermediate in the biosynthesis of (–)-fragin (**2.80a**), named valdiazen (**2.105**) was isolated and confirmed by chemical synthesis and X-ray crystal structure analysis. The isolated signaling molecule valdiazen (**2.105**) is racemic.

2.4 Biosynthetic Investigations of Fragin and Valdiazen

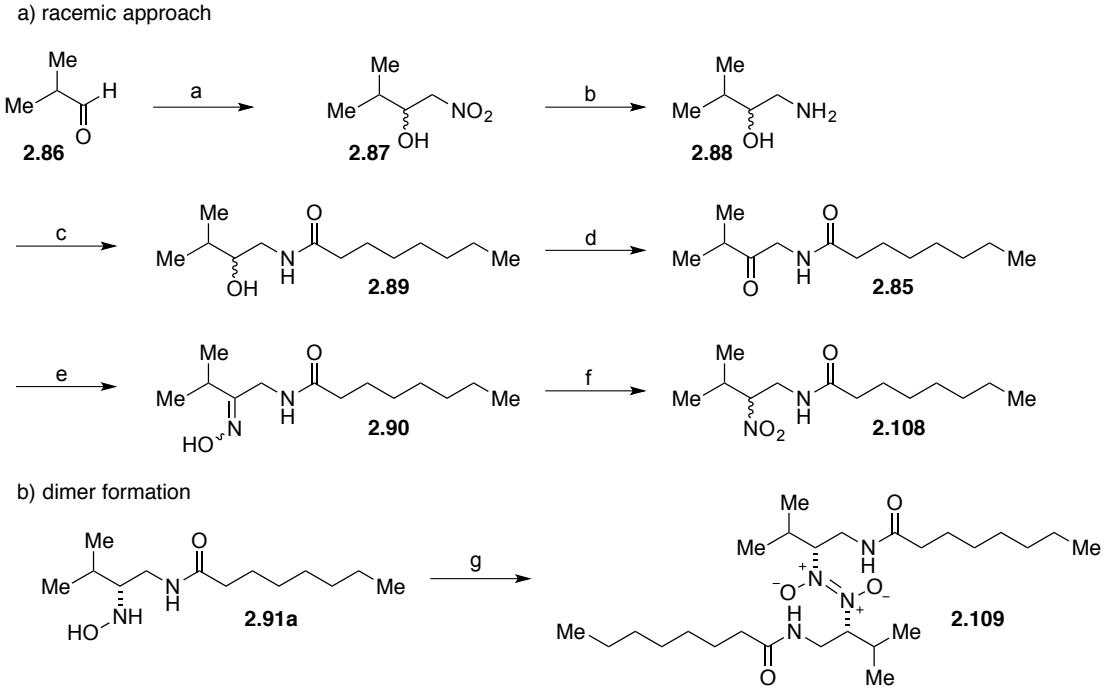
We followed a bio- and synthetic guided approach to identify possible intermediates in the biosynthesis of (–)-fragin (**2.80a**) and valdiazen (**2.105**). We first proposed biointermediates by retrosynthetic analysis of (–)-fragin (**2.80a**) and valdiazen (**2.105**). Synthetic samples were compared on their retention time and MS-pattern with the extract by HPLC-MS-analysis. Biological analysis and preparation of mutants were performed by Christian Jenul (Leo Eberl group, University of Zurich). Christophe Daeppen conducted synthetic aspects. Vidya Mannancherril is acknowledged for skillful technical support for the synthesis of biointermediates and a derivative of (–)-fragin (**2.80a**). Dr. Simon Sieber analyzed and compared the synthetic compounds by HPLC-MS measurements on their occurrence in the crude extracts of *Burkholderia cenocepacia H111* knock-out strains.

2.4.1 Synthesis of Biointermediates

The synthesis followed a modified racemic approach as described earlier by Tamura and co-workers (Scheme 2.19a).[91b] Starting from isobutyraldehyde (**2.86**), a Henry reaction with nitromethane and a catalytic amount of triethylamine furnished the nitroalcohol **2.87** in 94%. The nitro function was reduced under catalytic hydrogenation conditions to furnish the free amine to

[100] a) A. Murayama, S. Tamura, *Agr. Biol. Chem*. **1970**, *34*, 122; b) L. A. Dolak, T. M. Castle, B. R. Hannon, A. D. Argoudelis, F. Reusser, *J. Antibiot.* **1983**, *36*, 1425.

2.88. A peptide coupling reaction mediated by HATU and octanoic acid yielded the desired amide **2.89** in 79%. The alcohol was oxidized to the ketone **2.85** using DMP. As a side-product, the enolacetate was observed, which might result from a ketone protonation of the released acetic acid and subsequent nucleophilic attack on the acetyl moiety. IBX or neutral oxidizing conditions might be more suitable for this oxidation step. For our purpose, the obtained amount was enough to proceed further. In the last step the ketone **2.85** was reacted with hydroxylamine hydrochloride to form the desired oxime **2.90**. Nitro groups are found along with amines and hydroxylamines and could be a possible intermediate.[101] The nitro compound **2.108** was obtained by treating the oxime **2.90** with *m*-CPBA (Scheme 2.19b). Degradation studies by Tamura showed that (−)-fragin (**2.80a**) decomposes under acidic conditions to the nitroso-dimer **2.109**,[89] which was achieved by treating the hydroxylamine **2.91a** with *m*-CPBA to yield the nitroso-dimer **2.109** in a quantitative yield.



Scheme 2.19: Synthesis of proposed biointermediates**.** a) nitromethane, Et_3N, r.t., 14 h, 94%; b) Pd/C, H_2, MeOH, r.t., 30 h, 81%; c) HATU, DIPEA, octanoic acid, CH_2Cl_2/DMF, 0 °C to r.t., 24 h, 79%; d) DMP, CH_2Cl_2, r.t., 4 h, 46%; e) NH_2OH x HCl, NaOAc, MeOH, 70 °C, 2 h, yield n.d.; f) Na_2HPO_4, crushed urea, ACN, 90 °C, 30 min, then *m*-CPBA, 90 °C, 2h, 54%; g) *m*-CPBA, $CHCl_3$, 0 °C to r.t., 3 h, quant.

[101] J. Franke, K. Ishida, M. Ishida-Ito, C. Hertweck, *Angew. Chem. Int. Ed*. **2013**, *52*, 8271.

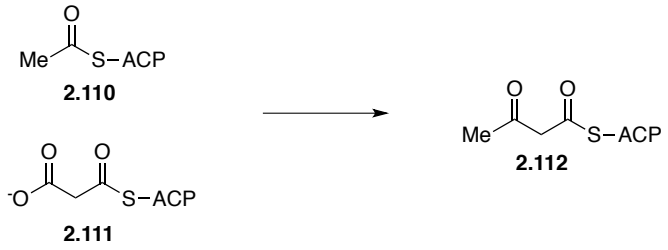
The synthesized intermediates were compared with the retention time and MS-pattern of the extracts of *Burkholderia cenocepacia H111*, by HPLC-MS analysis. The amine **2.101a**, hydroxylamine **2.91a** and oxime **2.90** could be confirmed to be present in the extract.[88] However only in low quantities. Therefore we assume that these products might be unstable under natural conditions or these products arise from degradation of fragin,[91b] and are not directly involved in the biosynthesis of the natural product.

2.4.2 Gene-Analysis

The gene-analysis of *Burkholderia cenocepacia* was performed by Christian Jenul. The following genes (named as ham = **h**uman **a**ntifungal **m**etabolite) were identified to be involved in the biosynthesis of fragin (**2.80**) and valdiazen (**2.105**) and their function are discussed in detail.

2.4.2.1 HamA: β-Ketoacyl Synthase

The enzyme is responsible for the chain growth of fatty acids. A malonate-unit **2.110** is first decarboxylated and binds then to acetyl-moiety of the acyl-carrier protein (ACP) **2.111** to form acetoacetyl ACP (**2.112**) (Scheme 2.20).[102]

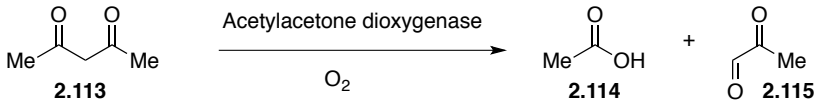


Scheme 2.20: Biological fatty acid synthesis.

[102] L. Du, C. Sánchez, B. Shen, *Met. Eng.* **2001**, *3*, 78.

2.4.2.2 HamB: Dioxygenase

Dioxygenases are transferring one or two units of oxygen on a substrate.[103] As an example is illustrated the cleavage of a diketone **2.113** to their corresponding carboxylic acid **2.114** and aldehyde **2.115** (Scheme 2.21)



Scheme 2.21: Oxidoreduction reaction.

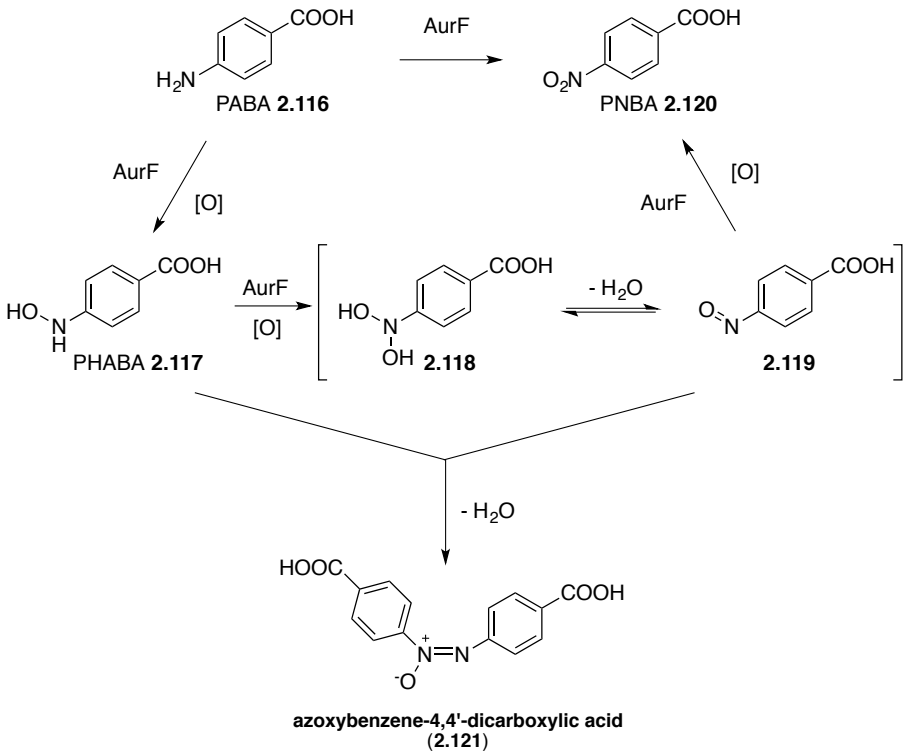
2.4.2.3 HamC: N-Oxygenase

The gene prediction for this enzyme is very similar to the enzyme AurF. This enzyme is able to oxidize aromatic amines to their oxyamines derivatives as shown in Scheme 2.22.[104] The enzyme belongs to a *di*-manganese mono-oxygenase species. The authors found also iron impurities (around 15%), which they could not exclude to be involved in the catalytic oxidation cycle.[105] AurF mediated the amine oxidation of PABA (**2.116**) to PHABA (**2.117**) and further to the intermediates dihydroxy amine **2.118** and nitrosobenzene intermediate **2.119.** Latter gets oxidized by AurF to PNBA (**2.120**). Furthermore, a recombination product of PHABA (**2.117**) and nitrosobenzene intermediate **2.119** was identified as azoxybenzene-4,4'-dicarboxylic acid (**2.121**).

[103] a) G. D. Straganz, A. Glieder, L. Brecker, D. W. Ribbons, W. Steiner, *Biochem. J.* **2003**, *369*, 573; b) G. D. Straganz, H. Hofer, W. Steiner, B. Nidetzky, *J. Am. Chem. Soc.* **2004**, *126*, 12202.

[104] a) R. Winkler, C. Hertweck, *ChemBioChem* **2007**, *8*, 973; b) *Angew. Chem. Int. Ed*. **2005**, *44*, 4083.

[105] G. Zocher, R. Winkler, C. Hertweck, G. E. Schulz, *J. Mol. Biol*. **2007**, *373*, 65.



Scheme 2.22: AurF catalyzed enzymatic *N*-oxidation.[104a] PABA = *p*-aminobenzoate (**2.116**); PHABA = *p*-hydroxylaminobenzoate (**2.117**); PNBA = *p*-nitrobenzoate (**2.120**).

2.4.2.4 HamD: NRPS

The non-ribosomal peptide synthase NRPS (Figure 2.15) represents a complex with diverse functionalities. Our cluster consists of:

- A: adenylation-domain (protein biosynthesis initiaton)
- PP domain: PCP domain (thiolation)
- R: Reductase (reduction to terminal aldehyde or alcohol)

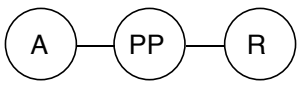


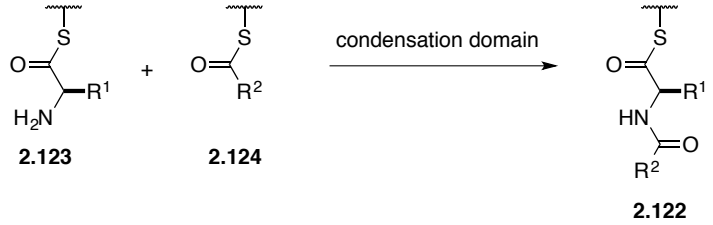
Figure 2.15: NRPS domain.

2.4.2.5 HamE: Unknown

The enzyme could not be assigned and the functionality in the biosynthesis remains unknown.

2.4.2.6 HamF: NRPS Condensation Domain

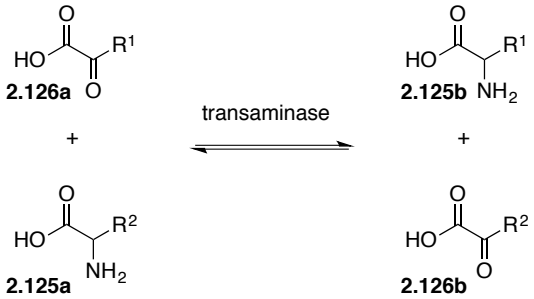
The NRPS condensation domain is responsible for the formation of an amide bond **2.122**, by the condensation of an amine **2.123** and thioester **2.124** (Scheme 2.23).[106]



Scheme 2.23: Condensation of two NRPS-bonded units.

2.4.2.7 HamG: Aminotransferase

Aminotransferases (transaminases) catalyzes the transfer of α-aminogroup (**2.125a** and **2.125b**) to an acceptor such as α-keto acids (**2.126a** and **2.126b**) as shown in Scheme 2.24.[107]



Scheme 2.24: Amine transfer on a carbonyl function and *vice versa*.

2.4.3 Proposed Biosynthesis of (–)-Fragin and Valdiazen

Feeding experiments with labeled ^{13}C-labeled (*R*)- and (*S*)-valine (**2.95a** and **2.95b**) showed incorporation of both amino acids. This means that the NRPS is not selective for (*R*)- or (*S*)-valine (**2.95a** and **2.95b**). HamF represents the condensation domain and might be involved in the fatty acid transfer. Knock-out experiments indicated that the gene hamB is not necessary for the production of (–)-fragin (**2.80a**). An explanation would be

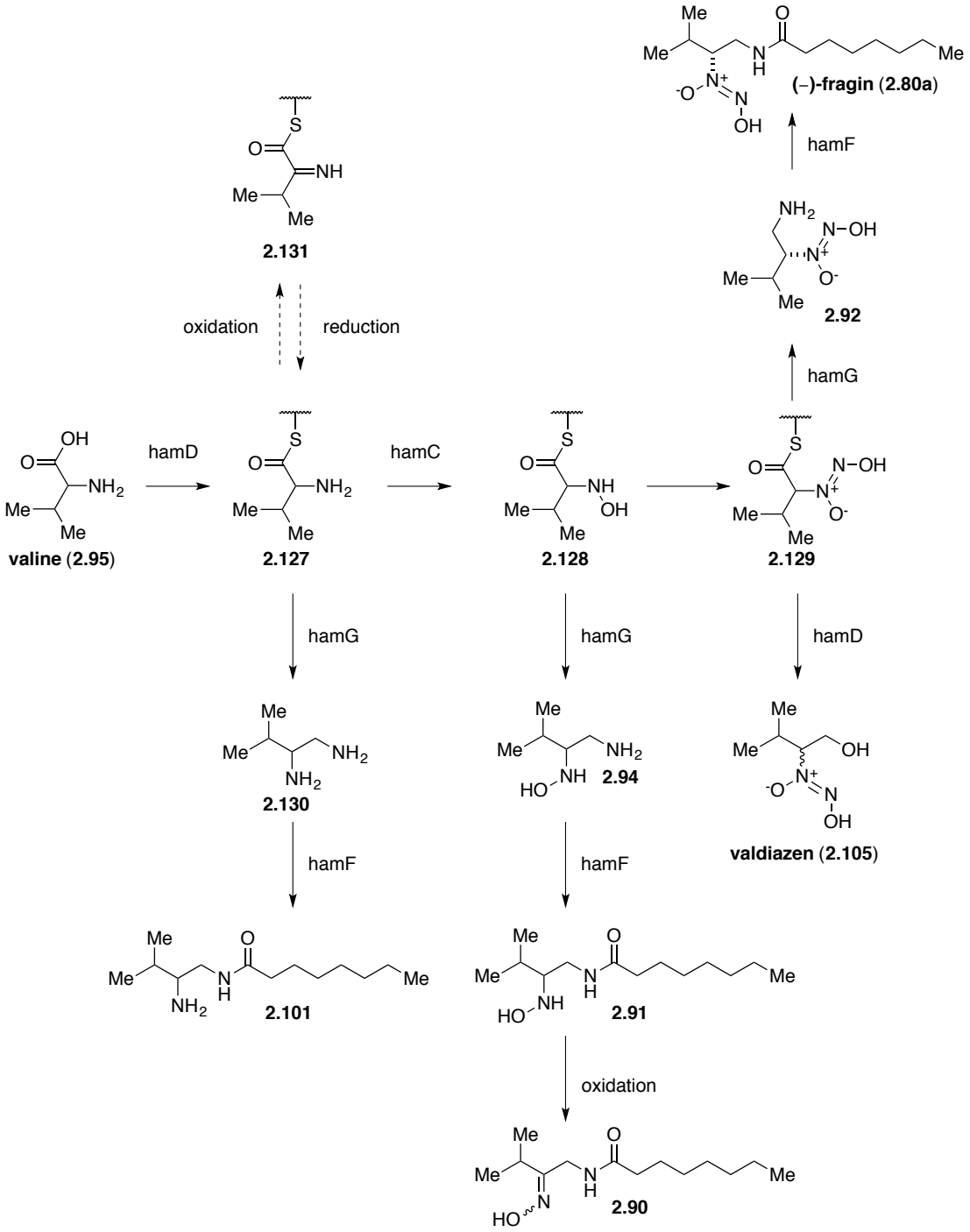
[106] E. S. Sattely, M. A. Fischbach, C. T. Walsh, *Nat. Prod. Rep*. **2008**, *25*, 757.

[107] F. Kudo, A. Miyanaga, T. Eguchi, *Nat. Prod. Rep*. **2014**, *31*, 1056.

that hamA and hamB are involved in the preparation of valine (**2.95**) and are therefore not mandatory for the (–)-fragin (**2.80a**) and valdiazen (**2.105**) biosynthesis. Based on this result, a biosynthetic pathway is proposed in Scheme 2.25.

First, valine (**2.95**) is attached by hamD to the NRPS to form thioester **2.127**. The free amine **2.127** is oxidized by hamC to the hydroxylamine **2.128**, which gets condensed with an unknown nitrogen source to the diazeniumdiolate functional group **2.129**. Out of this intermediate, two pathways might be possible for the synthesis of (–)-fragin (**2.80a**) and valdiazen (**2.105**). The reductive domain of hamD would release the molecule from the NRPS *via* an aldehyde intermediate, followed by a reduction directly valdiazen (**2.105**) would be formed.[108] If hamG is acting, the free amine **2.92** gets directly obtained *via* a reductive transaminase pathway.[108] The condensation domain hamF would finally attach the fatty acid chain on the amine **2.92** and the natural product (–)-fragin (**2.80a**) is formed. The found biosynthetic intermediates amine **2.101** and hydroxylamine **2.91** are probably formed by an early interaction of hamG and hamF by cleaving their corresponding amine **2.127** and hydroxylamine **2.128** on the NRPS *via* the intermediates **2.130** and **2.94**. The free hydroxylamine **2.91** is then oxidized to the oxime **2.90**. However, the gene hamE is not involved in our proposed biosynthetic pathway. The origin of the second nitrogen is still unclear and the racemic behavior of valdiazen can not be fully explained with our biosynthetic proposal. (–)-Fragin (**2.80a**) was isolated as an enantiopure material and the reaction of the fatty acid could be controlled by the NRPS surrounding and the chiral center, where only one epimer is preferred for the further synthesis of (–)-fragin (**2.80a**). The racemization itself can spontaneously take place on amine **2.127** or an oxidation could lead to an imine **2.131** intermediate and subsequently reduced back to the amine **2.127** in a non selective fashion as shown in Scheme 2.25.

[108] Y. Li, K. J. Weissman, R. Müller, *J. Am. Chem. Soc.* **2008**, *130*, 7554.



Scheme 2.25: Proposed biosynthesis of (–)-fragin (**2.80a**), valdiazen (**2.105**), amine **2.101**, hydroxylamine **2.91** and oxime **2.90**.

2.5 SAR-Studies of Fragin and Valdiazen

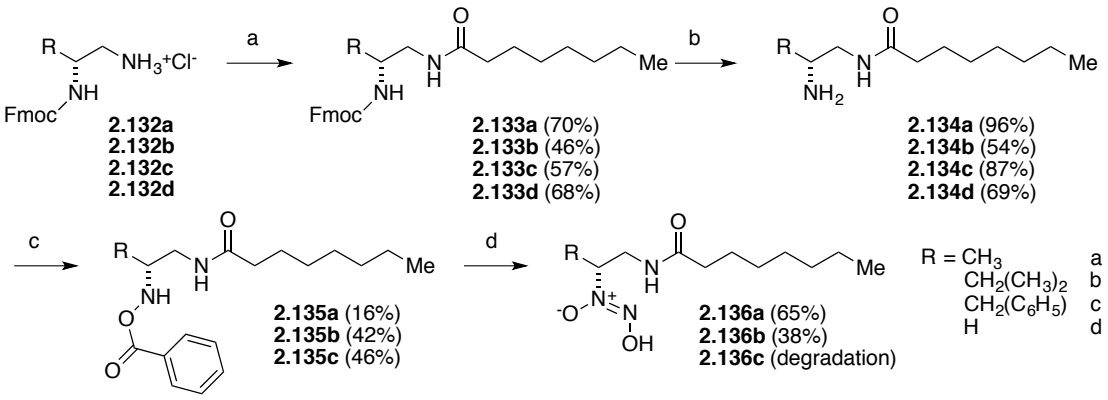
Several derivatives were synthesized and tested on their biological behavior. Christian Jenul performed the biological aspects (gene-sequencing and biological activity tests). Christophe Daeppen synthesized the fragin analogues. Vidya Mannancherril is acknowledged for the synthesis of a fragin derivative.

2.5.1 Derivative Synthesis

With the natural product in our hand, we were interested in the fragment, which is responsible for the antifungal activity. We started a SAR-study program by modifying the amino acid and fatty acid chain moiety. We further extended and investigated on the activity scope. The synthesis involved the same strategy as for the total synthesis of (–)-fragin (**2.80a**) and only modifications or problems will be discussed in detail.

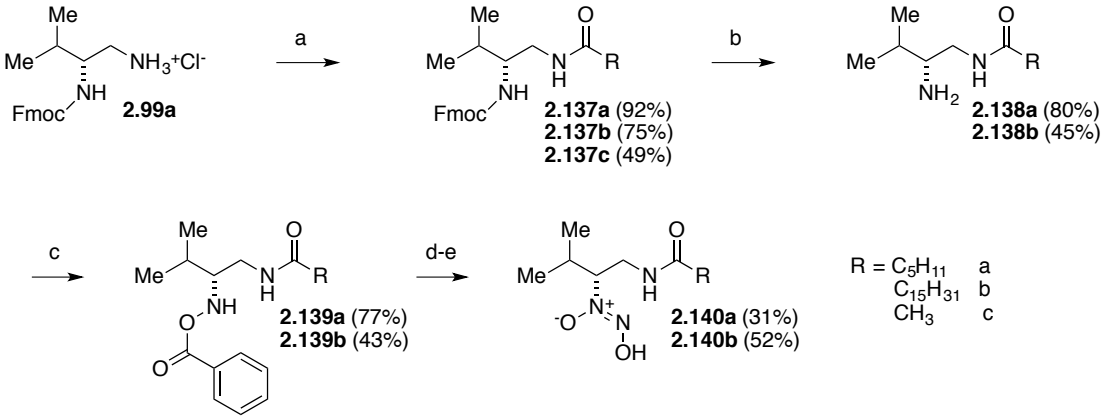
We started with the modification of the apolar amino acid residue by replacing the isopropyl function with other proteogenic amino acid (Scheme 2.26). Starting from the corresponding Fmoc-protected amino acids the ammoniumchloride salts **2.132a-d** were synthesized according to the procedure of Liskamp[92] using the modified conditions as described for the total synthesis of (–)-fragin (**2.80a**). The attachment of the fatty acid **2.133a-d** as well as the free amine intermediates **2.134a-d** were achieved in good yields and purity. The synthetic sequence proved to be robust also for other derivatives so far. However, huge variation in the reproducibility and yields were observed for the *N*-oxidation step. Unfortunately, the nucleophilic attack of the free amine **2.134d** occurred on the carbonyl and not on the peroxide moiety. The missing steric hindrance of the lacking alkyl functionality might support an attack on the peroxide moiety. Nevertheless, the molecules **2.135a-c** could be isolated in moderate yields. Due to the known instability of hydroxylamines, their isolation was omitted and the crude product was directly treated with isopentyl nitrite under basic conditions and the desired derivatives **2.136a** and **2.136b** were obtained in good yields. To our surprise, the

phenylalanine-analogue **2.136c** proofed to be unstable and was omitted for further studies.



Scheme 2.26: Synthesis of amino-fragin-derivatives. a) octanoyl chloride, DIPEA, DMAP, r.t., 14 h; b) $AlCl_3$, toluene, r.t., 3.5 h; c) dibenzoylperoxide, K_2HPO_4, THF, r.t., 21 h; d) N_2H_4 x H_2O, EtOH, r.t., 2.5 h, then isopentyl nitrite, $NH_{3(g)}$, EtOH, r.t., 0.5 h.

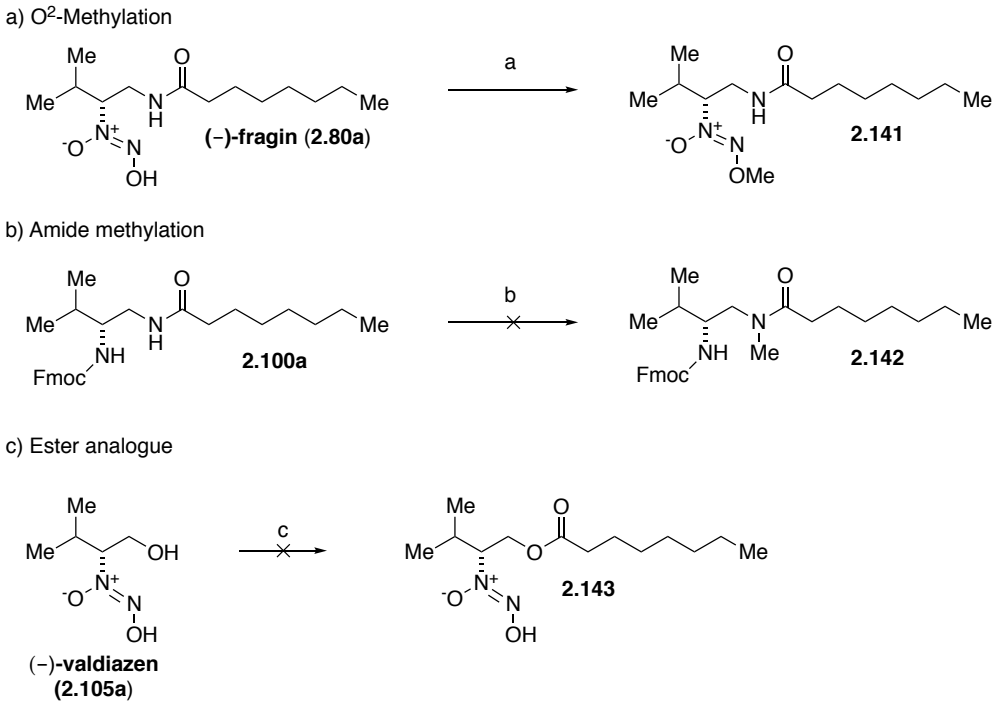
The fatty acids chain modifications (Scheme 2.27) were attached on the ammonium salt intermediate **2.99a** and the amides **2.137a-c** were obtained in good yields. The deprotection only worked for the substrates **2.137a** and **2.137b** to the corresponding free amine **2.138a** and **2.138b**. The other Fmoc-deprotection attempts using the elaborated $AlCl_3$ initiated Fmoc-deprotection for the substrates **2.137c** were not successful. No product could be isolated as well as NMR-analysis of the crude showed only starting material or decomposition. The substrate was not soluble in toluene, not even under high temperature or when additional $AlCl_3$ was added. The same insolubility was observed when standard conditions (piperidine or DBU) were used. We did not investigate further attempts for the deprotection of **2.137c**. The *N*-oxidation yielded the desired products **2.139a** and **2.139b** and upon benzoyl cleavage the hydroxylamine was used as crude without further purification. The crude was directly treated with isopentyl nitrite to the desired fatty acid chain modified molecules **2.140a** and **2.140b**.



Scheme 2.27: Synthesis of fatty acid-fragin-derivatives. a) octanoyl chloride, DIPEA, DMAP, r.t., 14 h, b) $AlCl_3$, toluene, r.t., 3.5 h; c) dibenzoylperoxide, K_2HPO_4, THF, r.t., 21 h; d) N_2H_4 x H_2O, EtOH, r.t., 2.5 h, then isopentyl nitrite, $NH_{3(g)}$, EtOH, r.t., 0.5 h.

Scheme 2.28 shows synthetic analogues of (–)-fragin (**2.80a**). Methylation using Me_2SO_4 and Na_2CO_3 as the base afforded the methylated-fragin **2.141** in a good yield. (Scheme 2.28a) The amide functionality **2.100a** was tried to be modified by an *N*-alkylation to form the methylated amide **2.142**, however it was not successful under the used conditions[109] and only the starting material could be recovered. Also under higher temperature, the molecule remained untouched (Scheme 2.28b). Steric hindrance from the Fmoc- and isopropyl part could inhibit the further transformation. It was also tried to replace the amide by an ester moiety (Scheme 2.28c). For this purpose, (–)-valdiazen (**2.105a**) was treated with octanoyl chloride and DIPEA to afford ester-fragin **2.143**, but only decomposition of the starting material was observed. The use of a coupling reagent might be more suitable for the sensitive diazeniumdiolate function.

[109] Q. Xia, X. Liu, Y. Zhang, C. Chen, W. Chen*, Org. Lett.* **2013**, *15*, 3326.



Scheme 2.28: Miscellaneous modifications. a) Me_2SO_4, Na_2CO_3, MeOH, 0 °C – r.t., 2.5 h, 71%; b) di-*tert*-butyl peroxide, Cu(I)Cl, chlorobenzene, 130 °C, 12 h; c) octanoyl chloride, DIPEA, DMAP, 14 h, r.t.

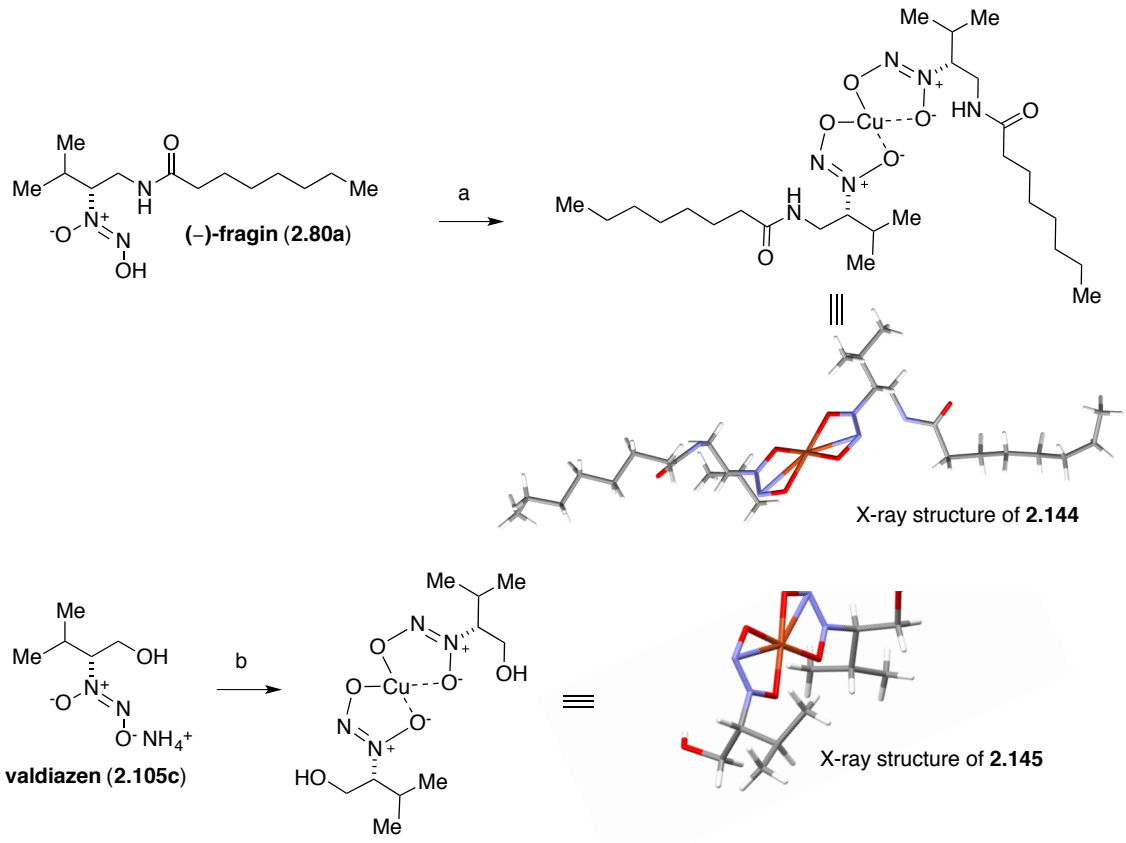
Initial results indicated an interaction of (–)-fragin (**2.80a**) with copper in a biological system.[110] We were highly interested in the complexing behavior of the natural products (–)-fragin (**2.80a**) and the ammonium derivative of valdiazen (**2.105c**)[111] to copper-metals and treated the corresponding natural products with $Cu(OAc)_2$ to obtain Cu-fragin (**2.144**)[90] and Cu-valdiazen (**2.145**) as blue solids (Scheme 2.29). Both tetradendate Cu-complex structures **2.144** and **2.145** were secured by X-ray crystal analysis (Scheme 2.29). A closer look on both crystal structures showed again the expected *cis*-conformation for the diazeniumdiolate group. The point group is C_2 for both structures. The arrangement of the ligands needs a few comments. Ligand exchanges in square planar complexes follow associate (S_N2-type) or dissociative (S_N1-type) mechanisms. After incorporation of the first ligand, the attack of the 2nd ligand can be influenced by the first ligand *via* the *trans*- or *cis*-effect. Such effects can be derived from crystal structure analysis by

[110] In collaboration with Dr. Dominic Hoepfner (Novartis Pharma AG), unpublished results.

[111] The ammonium salt is directly obtained as crude without further basic and acidic treatment.

estimation of the bond lengths in the crystal. The measured bonds are indicating shorter bonds for one diazeniumdiolate unit and longer bonds for the second diazeniumdiolate ligand. A clear indication cannot be derived from the bond lengths. If the focus is laid on the metal center and less on the ligand surrounding, a covalent bonded oxygen (1st ligand) is *trans* to a coordinating oxygen of the 2nd ligand. Electronic effects probably influence the arrangement of the ligands, which would indicate a *trans*-effect.[112] The UV-VIS spectra showed a maxima at 238 nm for Cu-fragin (**2.144**) and 237 nm for Cu-valdiazen (**2.145**).

[112] a) F. R. Hartley, *Chem. Soc. Rev*. **1973**, *2*, 163; b) J. V. Quagliano, L. Schubert, *Chem. Rev*. **1952**, *50*, 201.



Scheme 2.29: Synthesis of Cu-complexes **2.144** and **2.145** with (–)-fragin (**2.80a**) and valdiazen (**2.105c**) as ligands. a) $Cu(OAc)_2$, MeOH, r.t., 18 h, 91%; b) $Cu(OAc)_2$, MeOH, r.t., 15 h, 98%.

2.6 Biological Activity of Fragin- and Valdiazen-Derivatives

The biological activity tests were performed by Christian Jenul (Leo Eberl group, University of Zurich). All synthesized and tested derivatives are summarized in Figure 2.16. The effect of the stereocenter of fragin (**2.80a** and **2.80b**) and the diazeniumdiolate in its free methylated form **2.141** was tested (Figure 2.16a). The length of the fatty acid chain was shortened **2.140a** and enlarged **2.140b** (Figure 2.16b) as well as the amino acid residue was modified to a methyl-**2.136a** and an isobutyl group **2.136b** (Figure 2.16c). Valdiazen derivatives **2.105a** and **2.105b** were focused on the influence of the stereogenic center (Figure 2.16e). Cu-fragin complex (**2.144,** Figure 2.16d) and Cu-valdiazen complex (**2.145,** Figure 2.16f) were tested, if the diazeniumdiolate ligands will keep their activity bound in a complex.

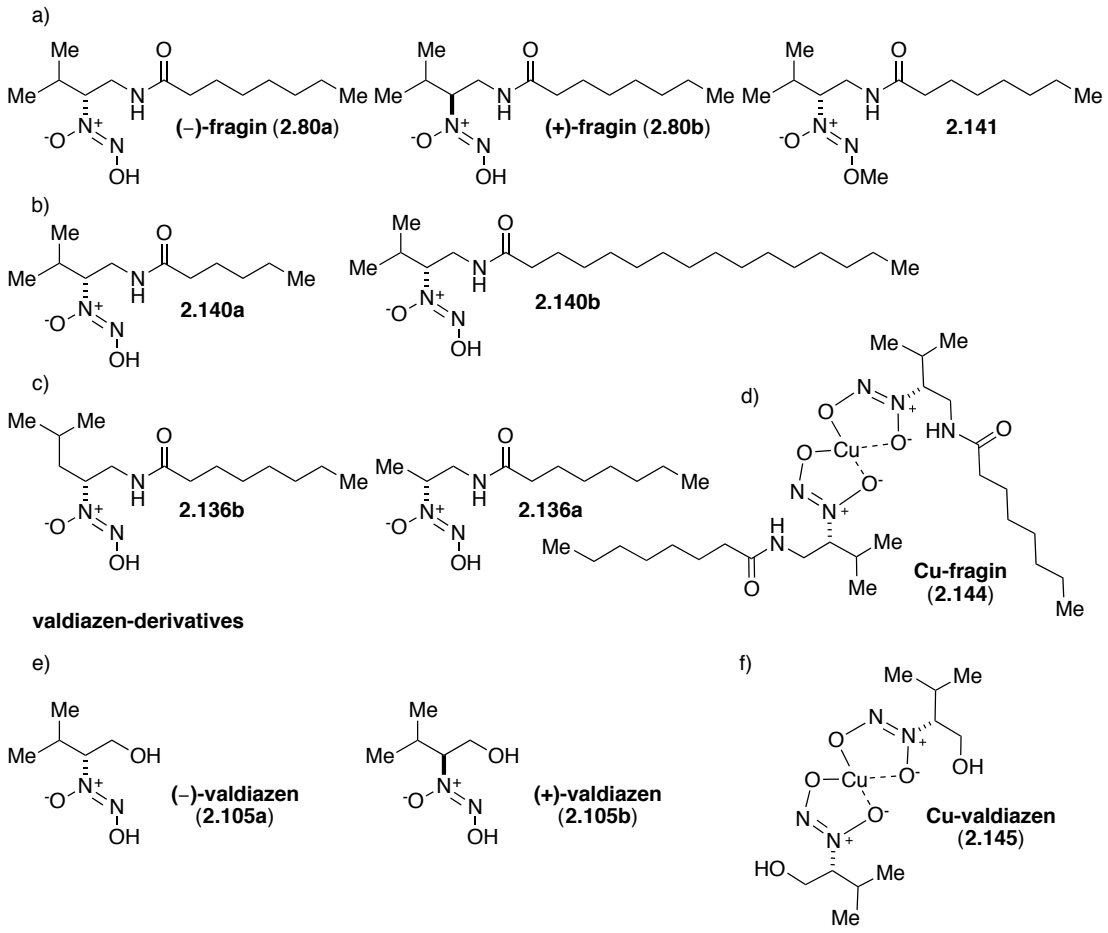


Figure 2.16: Overview of tested compounds in the bioassay.

A plate diffusion test was performed to evaluate the biological activity on Gram-positive (*Bacillus cereus, Staphylococcus aureus*) and Gram-negative bacteria (*Pseudomonas putida, Escheria coli, Klebsiella oxytoca*). These strains are either pathogenic or often found in the environment. The biological activities of the fragin (**2.80a** and **2.80b**) and valdiazen (**2.105**) analogues are summarized in table 2.3 (triplicates were conducted and the mean value was taken).

	Gram-pos. bacteria		Gram-neg. bacteria		
Derivative	***B. cereus***	***S. aureus***	***P. putida***	***E. coli***	***K. Oxytoca***
2.80a					
2.80b					
2.140a					
2.140b					
2.136a					
2.136b					
2.141					
2.144					
2.105a					
2.105b					
2.145					

Table 2.3: Activity test of fragin and valdiazen analogues (color code: green = 16 μg/ml, blue = 32 μg/ml, yellow = 64 μg/ml, orange = 128 μg/ml, red = no activity).

The tested diazeniumdiolates analogues and natural products (**2.80a**, **2.80b**, **2.105a**, **2.105b**, **2.136a**, **2.136b**, **2.140a**, **2.140b**, **2.141**, **2.144**, **2.145**) are not active against Gram-negative or only moderate against *E. coli*. Inhibition was observed for Gram-positive bacteria. Most interesting the chiral center has no influence on the activity (*R*)- and (*S*)-fragin (**2.80a** and **2.80b**), which was also the case for other chiral biological active *C*-diazeniumdiolates.[68] A closer look on the variable amino acid residue revealed comparable activity values for leucin-analogue **2.136b** and a decreased activity for alanine-analogue **2.136a**. A reason could be steric or

hydrophobic effects of the compounds. Based on an off-enzyme activity proposal, the amino acid residue is probably important for solubility or permeability reasons. This is also underlined for the shortened fatty acid analogue **2.140a**, which shows much less activity compared to the natural product **2.80a**. The elongated fatty acid product **2.140** has comparable activity to both fragin analogues (**2.80a** and **2.80b**). Fatty acid chains have important biological activities as they are involved in biofilm formation,[113] quorum sensing[114] or bioactive lipid mediators such as prostaglandins,[115] which influences invasive cancer progression, eicanosoids[116] with anti-inflammatory properties or sphingolipids[117] known for signaling and regulations in cell growth and death.

The methylated fragin **2.141** was totally inactive, which showed to be a strong indication that the diazeniumdiolate function must be the activity giving part of the molecule. The mode of action is unknown but cellular stress, due to complexation event might be a reason. In contrast, the Cu-fragin complex **2.144** is as well active. The results are in good agreement on earlier studies on the natural product dopastin (**2.72**).[68] The authors could demonstrate that dopastin (**2.72**) binds to a copper-enzyme and inhibits further reactions of the enzyme. Competing effects by adding Cu^{II}-salts showed no decrease in dopastin (**2.72**) activity, which suggest a preferred copper-enzyme affinity than to free Cu^{II}-salts, which could arise from a hydrophobic surface interaction of the enzyme. Surprisingly, the biointermediates (*R)*- and (*S)*-valdiazen (**2.105a** and **2.105b**) as well as the Cu-valdiazen complex **2.145** are

[113] C. N. H. Marques, D. G. Davies, K. Sauer, *Pharmaceuticals* **2015**, *8*, 816.

[114] a) W. T. Watson, T. D. Minogue, D. L. Val, S. Beck von Bodman, M. E. A. Churchill, *Mol. Cell* **2002**, *9*, 685; b) C. M. Waters, B. L. Bassler, *Annu. Rev. Cell Div. Biol*. **2005**, *21*, 319.

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[116] a) E. A. Dennis, P. C. Norris, *Nature Reviews* **2015**, *15*, 511; b) D. Stanley, *Annu. Rev. Entomol*. **2006**, *51*, 25.

[117] a) Y. A. Hannun, L. M. Obeid, *Nature Reviews* **2008**, *9*, 139; b) R. P. Rao, N. Vaidyanathan, M. Rengasamy, A. M. Oommen, N. Somaiya, M. R. Jagannath, *Journal of Lipids* **2013**, http://dx.doi.org/10.1155/2013/178910.

inactive for Gram-positive and Gram-negative bacteria. The more hydrophilic character was probably not able to enter the cell, which is underlined by the fact that the other tested fatty acid containing diazeniumdiolates are active for Gram-positive bacteria. Thus, the fatty acid chain might play an important roll in cellular uptake and penetration.

2.7 Conclusion and Outlook

In this chapter, the first enantioselective total synthesis of the natural product (–)-fragin (**2.80a**), a rare *C*-diazeniumdiolate containing molecule, was achieved in eight steps and an overall yield of 13%. The stereocenter could be assigned by chiral HPLC measuring to be (*R*)-configured. SAR-studies on (–)-fragin (**2.80a**) showed activity against Gram-positive and no activity against Gram-negative bacteria. The methylated diazeniumdiolate analogue **2.141** yielded in a complete inactivity, which shows that the diazeniumdiolate functional group is a main actor for antibiotic activity on Gram-positive bacteria. The cellular uptake is influenced by the hydrophobic surrounding, where an activity for all tested linear fatty acid chains **2.140a**-**b** and hydrophobic amino acid residues **2.136a**-**b** could be observed, but not for more polar sidechains (**2.105a**-**b**). A significant NO-release could not be observed by fluorescence spectroscopy.

Investigations on the biosynthesis of (–)-fragin (**2.80a**) brought a novel *C*-diazeniumdiolate compound, named valdiazen (**2.105**). The structure was elucidated by NMR-analysis and proofed by an enantioselective two step synthesis. The chiral center was determined by chiral-HPLC and compared with enantiopure synthetic (*R*)- and (*S*)-valdiazen (**2.105a** and **2.105b**), indicating that natural occurring valdiazen (**2.105**) is racemic. The compound showed no activity against Gram-positive and Gram-negative bacteria, probably due to the polar hydroxy group, which makes a cellular uptake not feasible.

A biosynthesis of (–)-fragin (**2.80a**) and valdiazen (**2.105**) was proposed based on labeled feeding experiment, isolation and characterization of (–)-fragin (**2.80a**) and the biosynthetic intermediate valdiazen (**2.105**). Feeding experiments with ^{13}C-labeled *(R)*- and (*S*)-valine (**2.105a** and **2.105b**) showed incorporation of both starting materials in the biosynthesis. However, (–)-fragin (**2.80a**) was isolated as enantiopure material and indicates that the attachment of the fatty acid part is preferred for one of the enantiomers. The synthesis of the diazeniumdiolate group is proposed to occur on the NRPS-cluster and then reductively cleaved to obtain valdiazen (**2.105**) or further condensated a fatty acid to form (–)-fragin (**2.80a**).

Cu-complexes of (–)-fragin (**2.80a**) and (–)-valdiazen (**2.105a**) were synthesized and secured by X-ray crystal structure analysis showing a 1:2 (host:guest) fashion. Applications of *C*-diazeniumdiolates should therefore be further investigated and considered as useful agents in metal-dependent diseases. The synthesis of bis-diazeniumdiolate molecules would probably increase the binding affinity and their applications for diseases and infection treatment should be tested.

3 Synthetic Studies Towards *Nor*-Sesquiterpenoid (2*R*)-Hydroxynorneomajucin

3.1 Neurodegenerative Diseases

The use of modern technology and pharmaceutical drugs have changed the way today's society lives. These circumstances have been greatly influenced by chemistry-based inventions like vaccines, insulin, caffeine, antibiotics or vitamins. An increased life expectancy has progressed from 48 years in the mid-20th century, to around 70 years today and an anticipated age of 76 years by the mid-21st century. [118] As a consequence, neurodegenerative diseases have become a serious health problem. The common feature of all neurodegenerative diseases is the degradation of neurons and therefore a slowly progressive loss of memory and cognitive functions. Today, over 46 million people are affected by dementia and that number is expected to increase to around 130 million by the year 2050.[119] This has an huge effect on health cost, which is estimated to be around 818 billion US-dollars and will further increase to a trillion by the year 2018. Mostly older people are affected by dementia. In the year 2010, around 4.7 million elderly people in the US were affected by dementia (> 65 years). This number will increase in the next years by a factor of three. Figure 3.1 shows the dementia distribution over the ages and demonstrates that dementia is associated or more evolved for the elderly.

[118] G. W. Leeson, *International Journal of Population Research* **2014**, Article ID 521523, doi:10.1155/2014/521523.

[119] Alzheimer's Disease International: World Alzheimer Report **2015**.

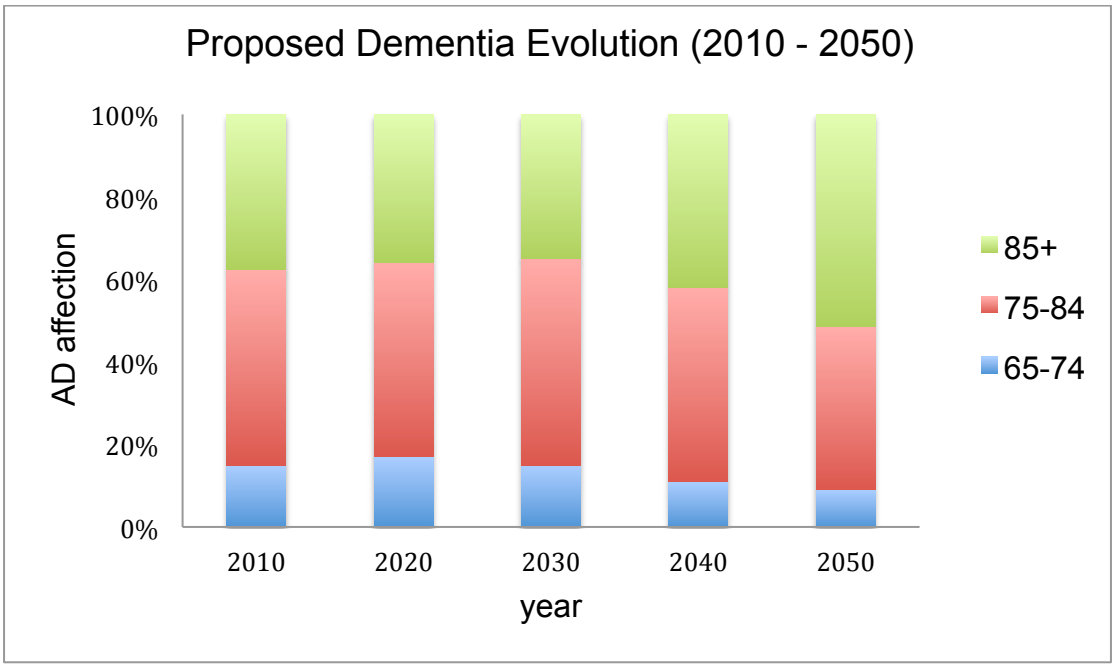

Figure 3.1: Age dependency for Alzheimer's disease evolution.

A successful treatment or therapy for neurodegenerative diseases has not been discovered even until today. Medications were developed to suppress symptoms and to increase life expectancy. The reason for the development of neurodegenerative diseases is still not fully understood. The most known diseases are Alzheimer's, Parkinson's, Huntington's diseases and amyotrophic lateral sclerosis (ALS).

3.1.1 Alzheimer's Disease

Alzheimer's disease is the most common neurodegenerative disease.[119] It was named and discovered after the german physician Dr. Alois Alzheimer, who discovered the disease in 1906. He observed a slow memory and that the cognitive function control worsened over time. He could prove his hypothesis by a postmortem brain analysis of a patient. He observed on the outside of neurons a collection of dense deposits or plaques and bands of fibres or tangles within the brain cells. An observation, which is still accepted as the definition for developing Alzheimer's. Today, the "plaques" have been identified as an accumulation of the protein fragment, β-amyloid (40-42 amino acids long), outside neurons in the brain and "tangles" as twisted strands of

the protein tau inside neurons.[120] A consequence of such aggregations is the damage or death of neurons.[121]

3.1.2 Parkinson's Disease

Parkinson's disease was first described by the english doctor James Parkinson in 1817 in his essay on shaking palsy, and later refined by Jean-Martin Charcot.[122] The disease is defined by an evolving movement disorder caused by a dopamine deficiency (death of dopaminergic neurons).[123] A common way to treat Parkinson's is to stimulate dopamine receptors.[124] It is considered that environmental and genetic factors are the main factors for Parkinson's disease, which makes an early diagnosis difficult.[125] Several genes[126] involved in oxidative stress, mitochondrial and proteosomal dysfunction were identified.[127] Disease characteristics include protein aggregrates[128] (α-synuclein with unknown function) inside nerve cells and the so-called Lewy bodies, discovered by the German-American neurologist Frederic Lewy in 1912.

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[120] a) G. B. Irvine, O. M. El-Agnaf, G. M. Shankar, D. M. Walsh, *Mol. Med*. **2008**, *14*, 451; b) A. Kumar, A. Singh, Ekavali, *Pharmacol Rep* **2015**, *67*, 195; c) H. W. Querfurth, F. M. LaFerla, *N. Engl. J. Med*. **2010**, *362*, 329.

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[126] a) C. Klein, M. G. Schlossmacher, *Nat. Clin. Pract. Neurol*. **2006**, *2*, 136; b) C. Klein, A. Westenberger, *Cold Spring Harb. Perspect Med*. **2012**, *2*, a008888, doi: 10.1101/cshperspect.a008888.

[127] W. Dauer, S. Przedborski, *Neuron* **2003**, *39*, 889.

[128] G. B. Irvine, O. M. El-Agnaf, G. M. Shankar, D. M. Walsh, *Mol. Med*. **2008**, *14*, 451.

3.1.3 Huntington's Disease

Huntington's disease was first described by George Huntington in 1872.[129] Mutations in the gene huntingtin yield an abnormally formed huntingtin protein. Characteristics include is a higher number (>36) of the *N*-terminal glutamine residue in the protein (encoded by the gene sequence cytosine-adenine-guanine (CAG)).[130] It acts directly as Huntington's disease indicator and predictor for Huntington's disease evolution (polyglutamic chain determines if a person will develop Huntington's disease).[131] The disease is hereditary and normally cognitive, motor, and psychiatric changes are observed. So far, only symptomatic drug treatments could be developed.[132]

3.1.4 Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (also known as Lou Gehrig's diseases, ALS or Charcot's disease, named after it's discoverer Jean-Martin Charcot) is a motor neuron disease that affects the nervous and muscles systems and yields in atrophy and weakness, spasticity and fasciculation. The origin of the disease is unknown, but might be influenced by failure in proteostasis, which results in protein misfolding[133] and cellular stress.[134] Identifications of several related genes and proteins support this fact, such as mutations in SOD1 (copper/zinc ion-binding superoxide dismutase).[135]

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[129] Huntington, G. On chorea. *Med. Surg. Rep.* **1872***, 26*, 320.

[130] G. B. Bates, R. Dorsey, J. F. Gusella, M. R. Hayden, C. Kay, B. R. Leavitt, M. Nance, C. A. Ross, R. I. Scahill, R. Wetzel, E. J. Wild, S. J. Tabrizi, N*ature Reviews Disease Primers 1*, **2015**, doi:10.1038/nrdp.2015.5.

[131] R. A. C. Roos, *Orphanet Journal of Rare Diseases* **2010**, *5*, 40.

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[133] S. Saxena, P. Caroni, *Neuron* **2011**, *71*, 35.

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3.1.5 Neurotrophins

The discovery of neurotrophins enabled the development of novel methods and strategies in neurobiology. The most prominent molecule is the nerve growth factor (NGF), first described by Elmer Bueker [136] and further investigated by Rita Levi-Montalcini and Stanley Cohen.[137] NGF is a protein complex (130 kDa) of three subunits: α-NGF, β-NGF and γ-NGF, where only the β-subunit (dimeric polypeptdide chain, 2 x 13 kDa) is responsible for neuroninduction. [138] This protein is responsible for the survival and proliferation of neuronal cells. In 1986, both scientists were awarded with the Nobel Prize in Physiology and Medicine for their discovery of growth factors. The term “neurotrophin” was introduced by Levi-Montalcini and her mentor Viktor Hamburger as a molecule, which induces cell survival or proliferation. NGF was then considered as a potential treatment source for Alzheimer’s and related neurodegenerative diseases,[139] where a common lack of NGF is observed.[140]

[136] E. D. Bueker, *Anat. Rec.* **1948**, *102*, 369.

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[140] F. Hefti, Ann. *Neurol.* **1983**, *13*, 109.

3.1.6 Receptors and Signaling Pathways

The involved enzymes, genes, pathways or other factors in neurodegeneration are by far more complex and still not fully understood. [138b, 141] A simplified signaling pathway is shown in Figure 3.2. Neurothrophins such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT3), neurotrophin 4 (NT4) or small molecules bind or interact with Trk (tropomyosin receptor kinase) or $p75^{NTR}$ (p75 neurotrophin receptor). Each TRK receptor binds selectively to a neurotrophin. NGF binds to TRKA, BDNF and NT4 bind to TRKB and NT3 binds to TRKC.[142] This interaction activates several cascades,[143] such as the phosphoinositide 3-kinase (PI3K)–AKT pathway [144], nuclear factor-κB (NF-κB), [145] mitogen-activated protein kinase (MAPK)[146] and the JUN *N*-terminal kinase (JNK).[147] TRK signaling is a tyrosine kinase-mediated pathway and promotes neurite outgrowth or cell survival.[148] The $p75^{NTR}$ pathways are more complex and involve cell survival, as well as cell death (apoptosis). The signaling pathway is influenced by the receptor expression and intracellular mediators and factors. GSK3 is a cell proliferation inhibitor and is often referred to as a potential target for future drug development in neurodegenerative[149] and other diseases.[150]

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[150] J. A. McCubrey, L. S. Steelman, F. E. Betrand, N. M. Davis, M. Sokolosky, S. L. Abrams, G. Montalto, A. B. D'Assoro, M. Libro, F. Nicoletti, R. Maestro, J. Basecke, D. Rakus, A. Gizak, Z. Demidenko, L. Cocco, A. M. Materlli, M. Cervello, *Oncotarget* **2014**, *5*, 2881.

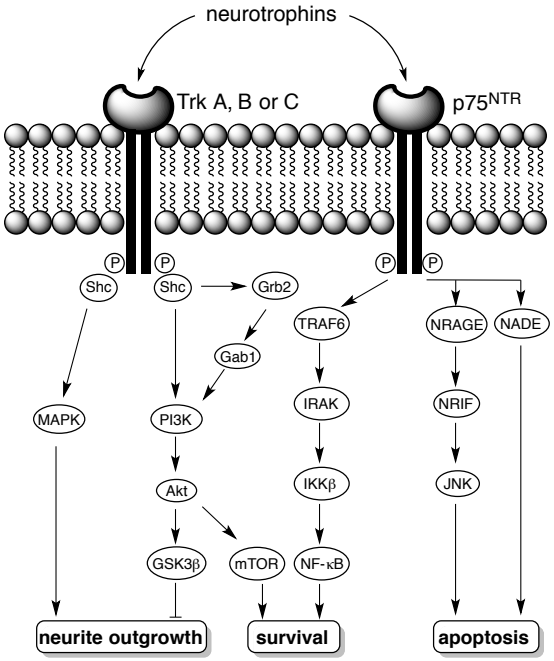

Figure 3.2: Neurotrophic cell signalling pathways; MAPK (mitogen-activatd protein kinase); Grb2 (Growth factor receptor-bound protein 2); Gab1 (GRB2-associated-binding protein 1); mTOR (mechanistic target of rapamycin); PI3K (phosphoinositide 3-kinase); Akt (Protein kinase-B (PKB)); IKKβ (inhibitor of nuclear factor kappa-B kinase subunit beta); NF-κB (nuclear factor-κB); JNK (JUN *N*-terminal kinase); TRK (tropomyosin receptor kinase); $p75^{NTR}$ (p75 neurotrophin receptor); GSK-3β, glycogen synthase kinase-3β; IRAK, interleukin-1 receptor-associated kinase; NADE, $p75^{NTR}$-associated cell death executor (NGFR); NRAGE, neurotrophin receptor-interacting MAGE homologue; NRIF, neurotrophin receptor-interacting factor; SHC, SRC homology domain-containing protein; TRAF6, TNF receptor-associated factor 6.

3.1.7 Natural Products as Potential Neuropharmaceuticals

Neuroinduction can be achieved by the stimulation of neurotrophin production or direct stimulation of a neurotrophin receptor (Trk or $p75^{NTR}$). However, a common problem in neurodegenerative treatment with potential agents is their stability towards physiological conditions, as well as their ability to cross the blood-brain-barrier (BBB)[151] where neuroinduction should ideally take place. The BBB is a highly selective permeable barrier (filter)[152] which prevents toxines, pathogens[153] and other compounds to enter the brain.[154] Furthermore, it separates the blood circulation from the central nervous system. Molecules, which contain a certain mass (>400 Da) and consist of eight or more hydrogen bonds are not able to pass this barrier[155] or have to be delivered *via* an active transport pathway.[156] 100% of large-molecules and <98% of small molecule drugs are not able to cross the blood-brain-barrier. Therefore there is a great interest to overcome this issue by using small organic molecules. Natural products are interesting lead structures as potent candidates.[157] Figure 3.3 shows an overview where natural products are used in neurodegenerative disease treatment.[158] It has to be mentioned that Alzheimer's is the most common neurodegenerative disease and therefore, of particular interest for the pharmaceutical industry and society.

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[151] a) J. Bicker, G. Alves, A. Fortuna, A. Falcão, *European Journal of Pharmaceutics and Biopharmaceutics* **2014**, *87*, 409; b) N. Weiss, F. Miller, S. Cazaubon, P.-O. Curaud, *Biochimica et Biophysica Acta* **2009**, *1788*, 842.

[152] E. E. Goldmann, *Beitr. klin. Chir*. **1909**, *64*, 192; *Abh. preuss. Akad. Wiss. Phys.-Math* **1913**, *1*, 1.

[153] J. A. Guttmann, B. B. Finlay, *Biochimica et Biophysica* **2009**, *1788*, 832.

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[155] W. M. Pardridge, *Drug. Discovery Today* **2007**, *12*, 54.

[156] a) B. V. Zlokovic, *Neuron* **2008**, *57*, 178; b) W. A. Banks, *BMC Neurology* **2009**, *9*, S3; c) W. Löscher, H. Potschka, *The Journal of the American Society for Experimental NeuroTherapeutics* **2005**, *2*, 86; d) S. Tietz, B. Engelhardt, *J. Cell Biol.* **2015**, *209*, 493.

[157] a) R. M. Wilson, S. J. Danishefsky, *Acc. Chem. Res*. **2006**, *39*, 539; b) Williams, A. Sorribas, M.-J. R. Howes, *Nat. Prod. Rep*. **2011**, *28*, 48; c) C. Tohda, T. Kuboyama, K. Komatsu, *Neurosignals* **2005**, *14*, 34.

[158] P. M. Joyner, R. H. Cichewicz, *Nat. Prod. Rep*. **2011**, *28*, 26.

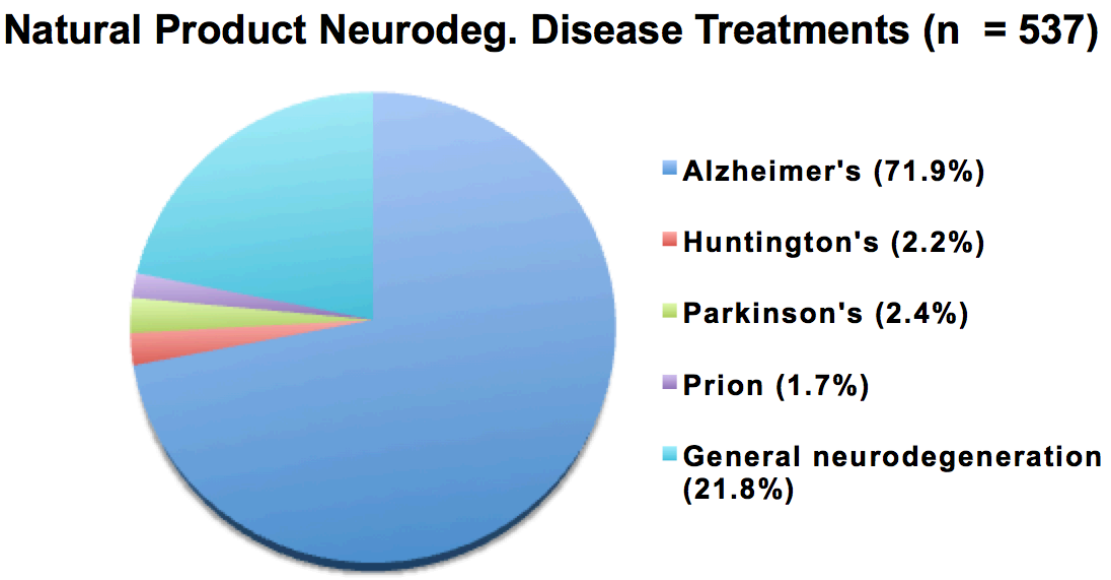

Figure 3.3: Natural Products and their applications in neurodegenerative disease treatment.[158]

Figure 3.4 illustrates the isolation source of natural products, which is dominated by plants.[158] The huge variability and number of plants makes them still one of the most interesting natural product sources. Nevertheless, fungi and bacteria bear enormous potential for drug discovery and are surprisingly less explored or considered.

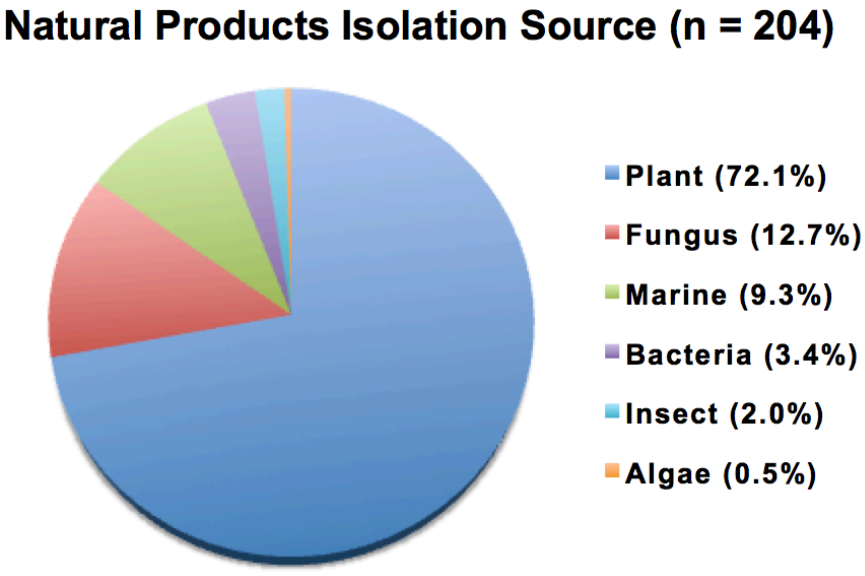

Figure 3.4: Origin of natural products.[158]

However, small quantities are obtained from isolation and makes further exploration of their potential as future anti-neurodegenerative drugs challenging. Chemists all over the world took into account this problem and work to provide various strategies towards these rather complex structures. The duty of total synthesis allows further an entry into the discovery of natural products analogues through SAR-studies. Figure 3.5 summarizes several very important isolated structures from nature, accessed through total synthesis.

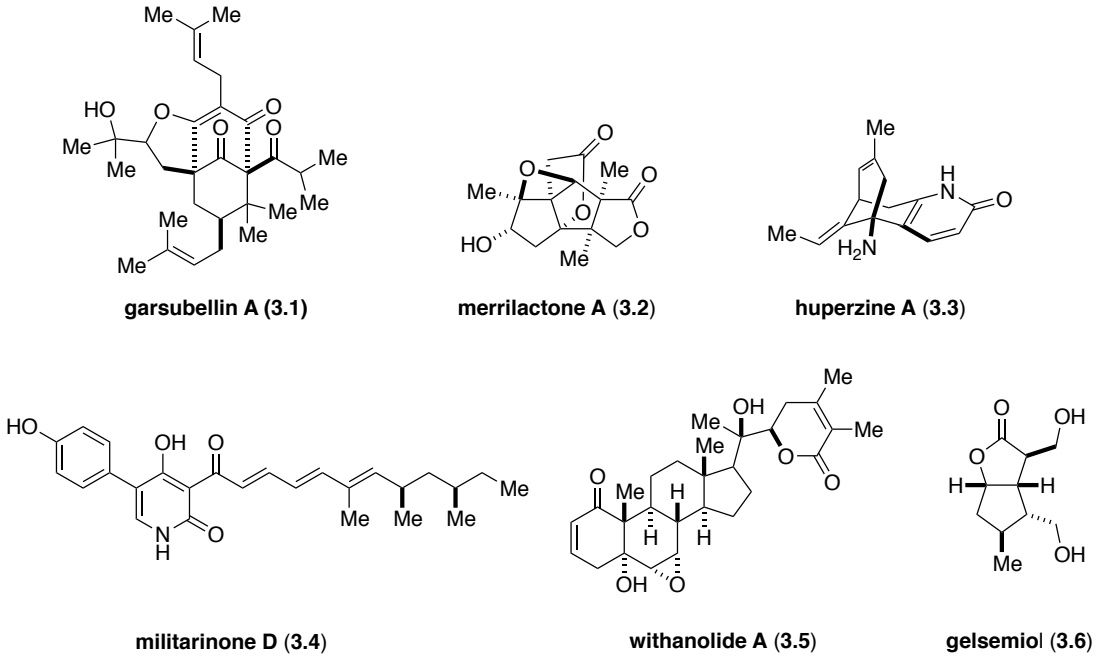

Figure 3.5: Neurotropic active natural products.

Polyprenylated acylphloroglucinols are charachteristic for their bicyclo[3.3.1]nonatrione motif and several groups have put their attention on it's complex structure such as garsubellin A (**3.1**).[159] Merrilactone A (**3.2**) is one of the most prominent molecules in neurodegenerative field and was isolated from the dried pericarps of *Illicium merrillianum* by Fukuyama and co-workers in 2000.[160] Merrilactone A (**3.2**) promotes neurite outgrowth in fetal rat cortical neurons at a concentration range of 0.1-10 *μ*M. It's high potency

[159] a) D. R. Siegel, S. J. Danishefksy, *J. Am. Chem. Soc*. **2006**, *128*, 1048; b) A. Kuramochi, H. Usuda, K. Yamatsugu, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc*. **2005**, *127*, 14200; c) N. M. Ahmad, V. Rodeschini, N. S. Simpkins, S. E. Ward, A. J. Blake, *J. Org. Chem*. **2007**, *72*, 4803.

[160] a) J.-M. Huang, R. Yokoyama, C.-S. Yang, Y. Fukuyama, *Tetrahedron Lett*. **2000**, *41*, 6111; b) J.-M. Huang, C.-S. Yang, M. Tanaka, Y. Fukuyama, *Tetrahedron* **2001**, *57*, 4691.

and unique structural oxetane feature clearly put this molecule in the focus of several natural product scientists.[161] Huperzine A (**3.3**) was isolated[162] in 1986 from the club moss *Huperzia serrate* and showed to act as a potent AChE inhibitor (82 nM).[163] This rather simple molecule consists of a complex molecular scaffold, which could be achieved by racemic and enantioselective syntheses.[164]

The Gademann group has contributed several neurotrophic natural products by total synthesis and investigated the neurite inducing properties of them. An extensively studied compound is militarinone D (**3.4**),[165] isolated from the mycelial extract of the entomopathogenic fungi *Paecilomyces militaris* by Hamburger and co-workers.[166] Comparable NGF activity (20 μM) and no cytotoxicity in PC12 cells using a lactate dehydrogenase assay was observed. The initial screening indicates that the activity is not linked to the length or the absolute configuration of the side chain. This study was then extended and truncated analogues were prepared for SAR-studies.[167] Interestingly, the study showed that indeed the fatty acid part is not responsible for the activity and the 4'-hydroxy function of the aromatic moiety

[161] a) V. B. Birman, S. J. Danishefsky, *J. Am. Chem. Soc*. **2002**, *124*, 2080; b) M. Inoue, T. Sato, M. Hirama*, J. Am. Chem. Soc.* **2003**, *125*, 10772; c) W. He, J. Huang, X. Sun, A. Frontier, *J. Am. Chem. Soc*. **2007**, *129*, 498; d) G. Mehta, S. R. Singh, *Angew. Chem. Int. Ed*. **2006**, *45*, 953; e) L. Shi, K. Meyer, M. F. Greany, *Angew. Chem. Int. Ed*. **2010**, *49*, 9250.

[162] a) J.-S. Liu, Y.-L. Zhu, C.-M. Yu, Y.-Z. Zhou, Y.-Y. Han, F.-W. Wu, B.-F. Qi, *Can. J. Chem*. **1986**, *64*, 837; b) W. A. Ayer, L. M. Browne, H. Orszanska, Z. Valenta, J.-S. Liu, *Can. J. Chem*. **1989**, *67*, 1538.

[163] a) Y. E. Yang, D. X. Yue, X. C. Tang, *Acta. Pharmacol. Sin*. **1986**, *7*, 110; b) X. C. Tang, P. De Sarno, K. Sugaya, E. J. Giacobini, *Neurosci. Res*. **1989**, *24*, 276; c) R. Wang, H. Yan, X.-C. Tang, *Acta Pharmacologica Sinica* **2006**, *27*, 1.

[164] a) R. Ding, B.-F. Sun, G.-Q. Lin, *Org. Lett*. **2012**, *14*, 4446; b) L. Qian, R. Ji, *Tetrahedron Lett.* **1989**, *30*, 2089; c) C. Lucey, S. A. Kelly, J. Mann, *Org. Biomol. Chem*. **2007**, *5*, 301; d) T. Koshiba, S. Yokoshima, T. Fukuyama, *Org. Lett*. **2009**, *11*, 5354.

[165] a) H. J. Jessen, A. Schumacher, T. Shaw, A. Pfaltz, K. Gademann, *Angew. Chem. Int. Ed*. **2011**, *50*, 4222; b) for a review see H. J. Jessen, K. Gademann, *Nat. Prod. Rep*. **2010**, *27*, 1168.

[166] K. Schmidt, U. Riese, Z. Li, M. Hamburger, *J. Nat. Prod*. **2003**, *66*, 378.

[167] F. Schmid, H. J. Jessen, P. Burch, K. Gademann, *Med. Chem. Commun*. **2013**, *4*, 135.

is essential for the activity. These so called truncated analogues were shown to be equal or more potent as the natural lead structure **3.4**.[168]

Withanolide A (**3.5**) was isolated from *Withania somnifera* ("Ashwagandha" in Ayurveda or Indian ginseng), a plant used in traditional Indian medicine. A total synthesis[169] and SAR-studies[170] were performed and the activity was tested on human SH-SY5Y cells. These studies could identify slightly more potent withanolide analogues and concluded that the size rather than the functionality attached on the A-ring is important.

Gelsemiol (**3.6**) posseses an iridoid[171] structure and was isolated from *Gelsemium sempervirens* (Gentianales)[172] and analogues from *Verbena littoralis* (Lamiales).[173] The enantioselective total synthesis was achieved in an impressive nine step synthesis with an overall yield of 14%.[174] Gelsemiol induced neurite outhgrowth moderately. In contrast, it showed a higher potency in combination with NGF as the sole NGF control.

Furthermore, several molecules are already approved by the FDA for neurodegenerative disease treatments and available on the market, as shown in Figure 3.6. Rivastigmine (**3.7**) is a reversible cholinesterase inhibitor used

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168 E. A. Crane, K. Gademann, *Angew. Chem. Int. Ed*. **2016**, *55*, 2.

169 C. K. Jana, J. Hoecker, T. M. Woods, H. J. Jessen, M. Neuburger, K. Gademann, *Angew. Chem. Int. Ed.* **2011**, *50*, 8407.

170 R. Liffert, J. Hoecker, C. K. Jana, T. M. Woods, P. Burch, H. J. Jessen, M. Neuburger, K. Gademann, *Chem. Sci*. **2013**, *4*, 2851.

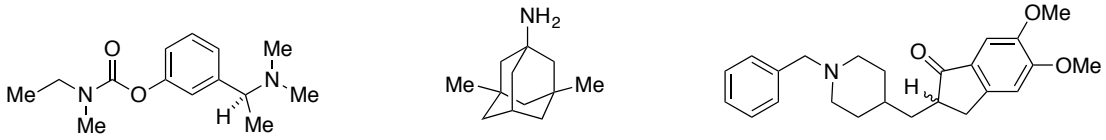
171 a) C. A. Boros, *J. Nat. Prod*. **1990**, *53*, 1055; b) L. J. El-Naggar, J. L. Beal, *J. Nat. Prod.* **1980**, *43*, 649; c) B. Dinda, S. Debnath, R. Banik, *Chem. Pharm. Bull. 1011,* **59**, 803.

172 S. R. Jensen, O. Kirk, B. J. Nielsen, *Phytochemistry* **1987**, *26*, 1725.

173 a) Y.-S. Li, K. Matsunaga, R. Kato, Y. Ohizumi, *J. Pharm. Pharmacol*. **2001**, *53*, 915; b) Y. Li, M. Ishibashi, M. Satake, Y. Oshima, Y. Ohizumi, *Chem. Pharm. Bull*. **2003**, *51*, 1103; c) Y. Li, Y. Ohizumi, *Yakugaku Zasshi* **2004**, *124*, 417.

174 P. Burch, M. Binaghi, M. Scherer, C. Wetzel, D. Bossert, L. Eberhardt, M. Neuburger, P. Scheiffele, K. Gademann, *Chem. Eur. J.* **2013**, *19*, 2589.

for mild to moderate Alzheimer diseases.[175] Memantine (**3.8**) acts as a NMDA receptor inhibitor (glutamate-agonist) and used in the treatment of moderate-to-severe Alzheimer diseases. [176] Donepezil (**3.9**) is a reversible cholinesterase inhibitor and used for mild to moderate Alzheimer diseases.[177]



rivastigmine (**3.7**) **memantine** (**3.8**) **donepezil** (**3.9**)

Figure 3.6: FDA-approved anti-Alzheimer's disease medication.

3.1.8 A source of Natural Neuroinducers - The genus *Illicium* (*Illiciaceae*)

The genus *Illicium* contains 42 species and belongs to the family of *Illiciaceae*. Over 70% of *Illicium* species are found in southwestern and eastern Asia. The star-anise fruit (*Illicium verum*) is used for seasoning in Chinese and Southeast Asian food. [178] Most *seco*-prezizaane type sesquiterpenes were isolated from the genus *Illicium*. The most active majucin-type sesquiterpenes were isolated from *Illicium jiadifengpi.* The structure of (−)-jiadifenolide (**3.10**),[179] jiadifenin (**3.11**),[180] (2*S*)-hydroxy-3,4-dehydro-neomajucin (**3.12**)[180], jiadifenoxolane A (**3.13**),[179] (2*R*)-hydroxynor-neomajucin (**3.14**)[181] and ODNM (**3.15**) [180] are presented in Figure 3.7. The neurite enhancement ability was tested in primary cultures of fetal rat cortical neuron cells with NGF as the positive control.

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[175] a) B. R. Williams, A. Nazarians, Mark. A. Gill, *Clinical Therapeutics* **2003**, *25*, 1634; b) J. S. Birks, L. Y. Chong, J. Grimley Evans *Cochrane Database Syst Rev*. **2015**, 22, CD001191. DOI:10.1002/14651858.CD001191.pub4

[176] S. J. Thomas, G. T. Grossberg, *Clinical Interventions in Aging* **2009**, *4*, 367.

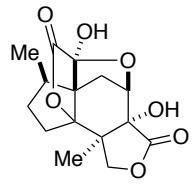
[177] J. Birks, R. J. Harvey, *Cochrane Database Syst Rev.* **2006**, *25*, CD001190. DOI: 10.1002/14651858.CD001190.pub2

[178] J.-M. Huang, H. Liu, C. Yang, J. Ye, Y. Xue, *Chin. Trad. Herb. Drugs* **2000**, *31*, 54.

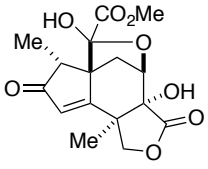
[179] M. Kubo, C. Okada, J.-M. Huang, K. Harada, H. Hioki, Y. Fukuyama, *Org. Lett.* **2009**, *11*, 5190.

[180] R. Yokoyama, J.-M. Huang, C.-S. Yang, Y. Fukuyama, *J. Nat. Prod.* **2002**, *65*, 527.

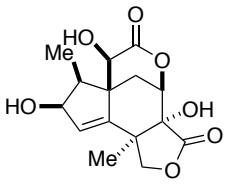
[181] M. Kubo, K. Kobayashi, J.-M. Huang, K. Harada, Y. Fukuyama, *Tetrahedron Lett.* **2012**, *53*, 1231.



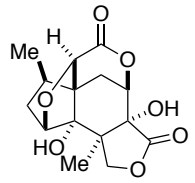
(–)-jiadifenolide (**3.10**)
0.01–10 μM



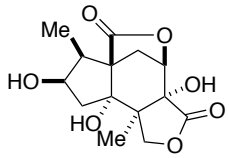
jiadifenin (**3.11**)
0.1–10 μM



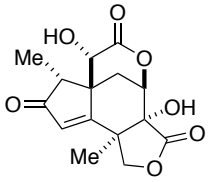
(2*S*)-hydroxy-3,4-dehydroneomajucin (**3.12**), 10 μM



jiadifenoxolane A (**3.13**)
0.01–10 μM



(2*R*)-hydroxynorneomajucin (**3.14**)
1–10 μM

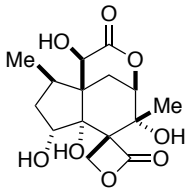


ODNM (**3.15**)
0.1 μM

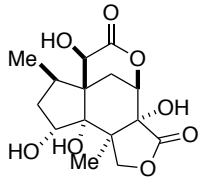
Figure 3.7: Neutrophic majucin-type sesquiterpenes.

3.1.9 Biosynthesis of *Seco*-Prezizaane Sesquiterpenes

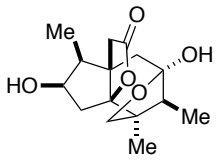
Seco-prezizaanes have shown to be highly active as neurotropic mediators. Six classes are known and are distinguished by their skeletal scaffold **3.16** as shown in Figure 3.8. These bicyclic AB-scaffolds consist of a highly oxidized 15-carbon unit. The subunits are called anisatin- (**3.17**), majucin- (**3.18**), pseudomajucin- (**3.19**), pseudoanisatin- (**3.20**), minwanensin- (**3.21**) and cycloparvifloralone-type (**3.22**) sesquiterpenes.



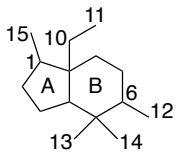
anisatin (**3.17**)



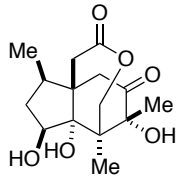
majucin (**3.18**)



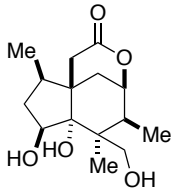
pseudomajucin (**3.19**)



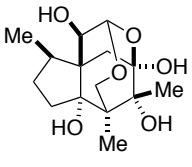
seco-prezizaane **3.16**



pseudoanisatin (**3.20**)



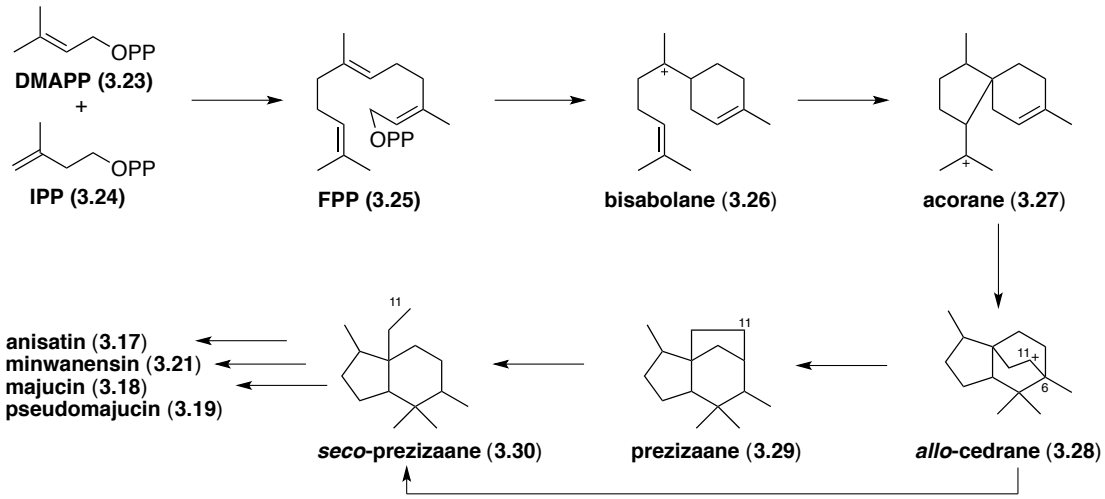
minwanensin (**3.21**)



cycloparvifloralone (**3.22**)

Figure 3.8: *Seco*-prezizaane classes and skeletal numbering.

The synthesis of terpenes (and sesquiterpenes) is derived from DMAPP (**3.23**) and IPP (**3.24**) and, upon condensation, farnesol pyrophosphate (FPP, **3.25**) is formed (Scheme 3.1). Releasing of the pyrophosphate moiety forms an allyl-cationic-species, which is attacked intramolecularly by the olefin to form bisabolane (**3.26**). The formed tertiary cation undergoes a 1,2-hydride shift to a cyclic tertiary cationic species (not shown). The acorane intermediate **3.27** is formed by a second intramolecular attack of the geminal methyl-containing olefin. A third rearrangement takes place, which forms the key intermediate *allo*-cedrane (**3.28**). Out of this structure, a variety of natural products are synthesized *via* this intermediate. Upon cleavage of the C-6/C-11 bond, the prezizaane (**3.29**) or *seco*-prezizaane (**3.30**) core structure is formed, from which neurotrophic active molecules are formed such as anisatin (**3.17**) or majucin (**3.18**).[182]



Scheme 3.1: Biosynthesis of *seco*-prezizaane type structures.

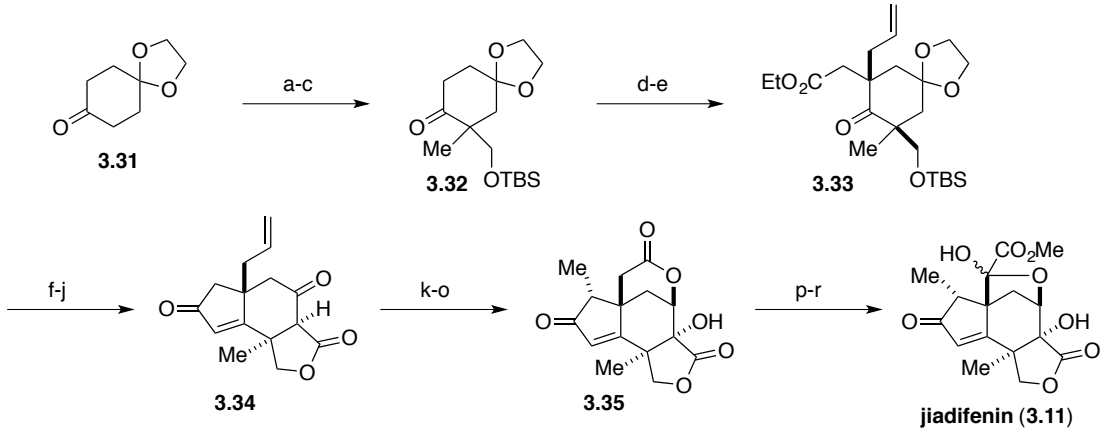
[182] Y. Fukuyama, J.-M. Huang, *Studies in Natural Products Chemistry*, A. Rahman, Ed.; Elsevier: New York, **2005**, *32*, 395.

3.2 Previous Total Syntheses of Majucin-Type Sesquiterpenes

3.2.1 Danishefsky's Total Synthesis of (±)-Jiadifenin

Danishefsky and co-workers published the first total synthesis of a majucin-type natural product in 2004. They could achieve the total synthesis of (±)-jiadifenin (**3.11**) in 18 linear steps with an overall yield of 1.9% (Scheme 3.2).[183] The synthesis started with the commercially available cyclohexanone **3.31**, which represents the B-ring of the natural product. A desymmetrization of **3.31,** was achieved by methylation with MeI, followed by hydroxymethylation with formaldehyde to install the β-hydroxy group, which was directly TBS-protected to afford **3.32** in 64% yield over three steps. A sequential allylation and carboethoxymethylation yielded the ester **3.33** in a diastereomeric ratio of 3:1. Conversion of the ester moiety to a β-ketophosphonate followed by an intramolecular HWE-reaction and global deprotection furnished the desired cyclopentenone **3.34**. The C-ring lactone was achieved by an intramolecular Claisen-condensation. Oxidation with *m*-CPBA afforded the α-hydroxylated β-ketolactone and subsequent ketone reduction with $NaBH_4$ furnished the alcohol in a completely diastereoselective manner. Methylation at C-1 followed by ozonolysis of the terminal alkene and subsequent Jones oxidation led to the ABCD bislactone ring system **3.35.** A Luche reduction of the enone, followed by a α-hydroxylation of the D-ring using Davis's oxaziridine afforded the α-hydroxy-lactone and finally a Jones oxidation afforded the natural product (±)-jiadifenin (**3.11**).

[183] Y. S. Cho, D. A. Carcache, Y. Tian, Y.-M. Li, S. J. Danishefsky, *J. Am. Chem. Soc.* **2004**, *126*, 14358.



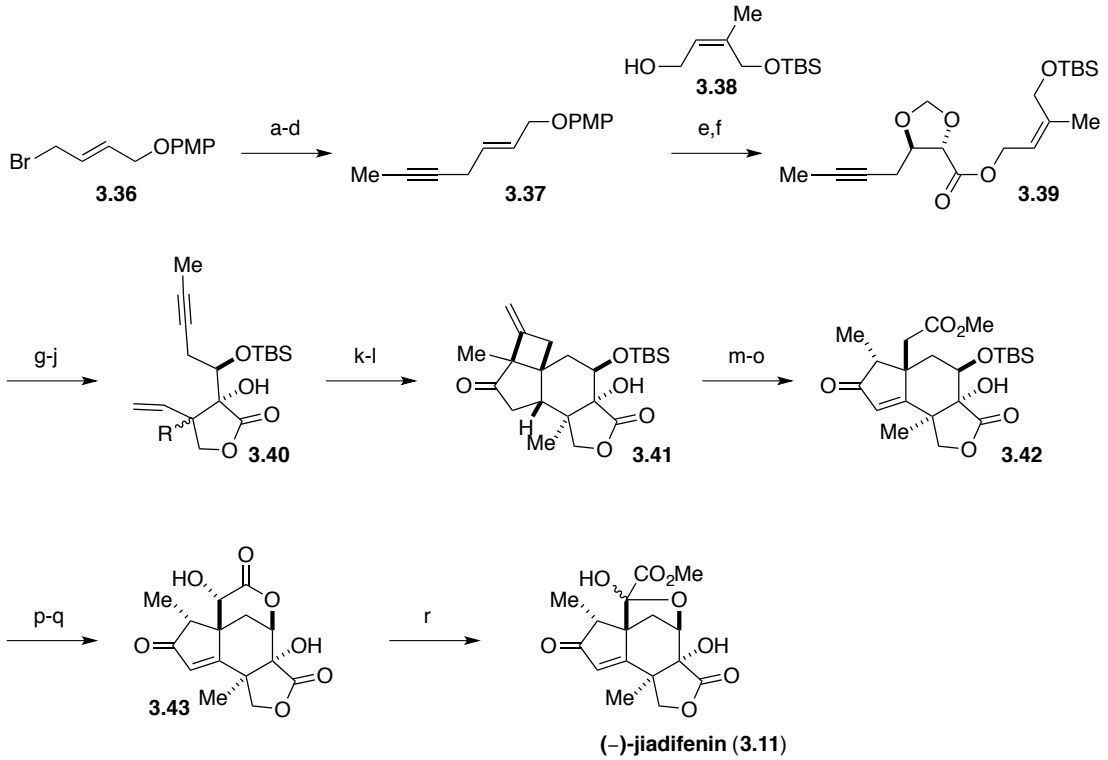
Scheme 3.2: Total synthesis of (±)-jiadifenin (**3.11**) by Danishefsky and co-workers. a) LiHMDS, THF, –78 °C, MeI, –78 °C to r.t.; b) 10% KOH, MeOH, aq. HCHO, 0 °C; c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 64% (over three steps); d) LiHMDS, THF, –78 °C; allyl bromide, –78 °C to r.t., 73%; e) LDA, THF, –78 °C to –20 °C, $BrCH_2CO_2Et$, HMPA, –78 °C, 97%, *d.r.* = 3:1; f) $LiCH_2P(O)(OMe)_2$, THF, –78 °C, 81%; g) NaH, THF, reflux, 91%; h) 2 M HCl, THF, 94%, i) $ClCO_2Et$, py, DMAP, CH_2Cl_2, 0 °C to r.t., 93%; j) NaH, THF, reflux, 94%; k) *m*-CPBA, CH_2Cl_2, 90%; l) $NaBH_4$, THF/MeOH (1:1), –78 °C, 93%; m) LDA, THF, –40 °C to –15 °C, MeI, HMPA, –35 °C, 64% (over two steps); n) O_3, Sudan 7B Red, CH_2Cl_2/EtOH (1:1), –78 °C; o) Jones reagent, acetone, 90%; p) $NaBH_4$, $CeCl_3 \times 7\ H_2O$, THF/MeOH (3:1), –65 °C, 88%; q) NaHMDS, THF, –78 °C, Davis' oxaziridine, THF, –78 °C, 42% (over two steps); r) Jones reagent, acetone; MeOH, 40%.

3.2.2 Zhai's Enantioselective Total Synthesis of (–)-Jiadifenin

Zhai and co-workers reported on an enantioselective route to (–)-jiadifenin (**3.11**, Scheme 3.3).[184] The allylic bromide **3.36** was first treated with lithiated propyne to form the enyne **3.37**, followed by a Sharpless asymmetric dihydroxylation to the diol in 93% *ee*, which was protected by an acetal group to the dioxolane. The PMP-protecting group was cleaved and the free alcohol was oxidized under Jones conditions to the carboxylic acid. An esterification with the alcohol **3.38** furnished precursor **3.39**, ready for the Ireland-Claisen rearrangement (*d.r.* = 7:1). An acid-promoted lactonization, followed by dioxolane deprotection and TBS protection of the secondary alcohol furnished the enyne **3.40**. An intramolecular Pauson-Khand reaction formed the cyclopentenone, which was irradiated in the presence of allene to form the

[184] Y. Yang, X. Fu, J. Chen, H. Zhai, *Angew. Chem. Int. Ed*. **2012**, *51*, 9825.

[2 + 2] photoadduct **3.41**. An ozonolysis with NaOMe cleaved the terminal olefin to the methyl ester and the enone **3.42** was formed *via* a Saegusa-Ito reaction. Silyl deprotection using TBAF yielded directly in the lactone, which was α-hydroxylated in the presence of NaHMDS and Davis' oxaziridine to form lactone **3.43**. Finally, Jones oxidation furnished (–)-jiadifenin (**3.11**) in 18 steps and 0.7% overall yield from allylic bromide **3.36**.



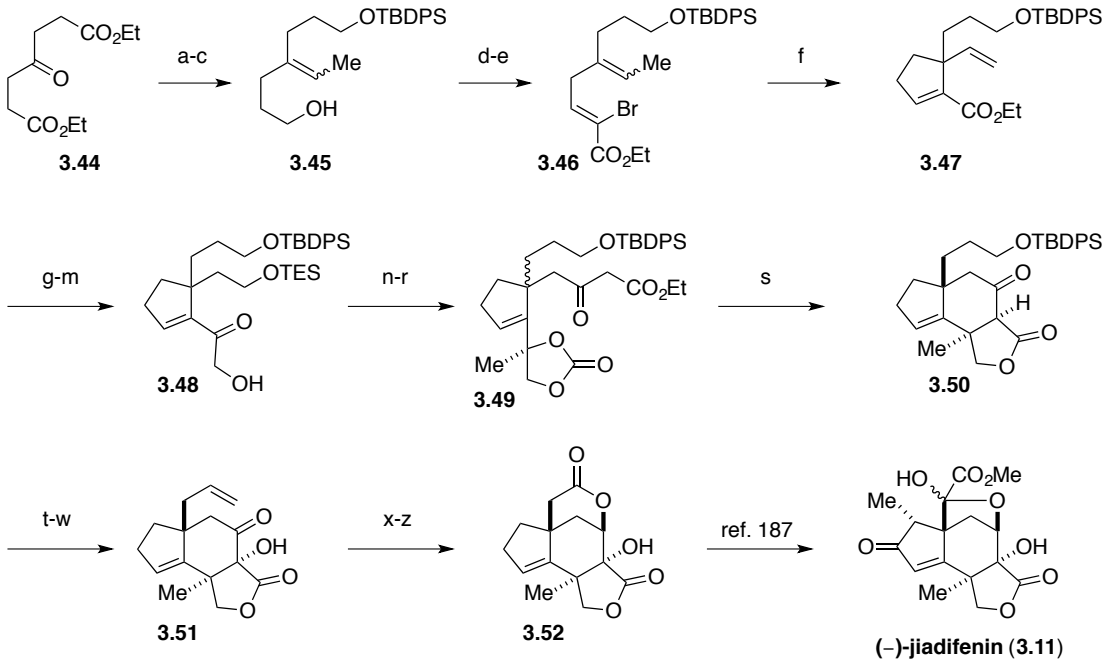
Scheme 3.3: Zhai's synthesis of (–)-jiadifenin. a) 1-Bromo-1-propene, *n*-BuLi, CuI, THF, –78 °C to r.t., 74%; b) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), 0 °C, 95%, >93% *ee*; c) KOH, CH_2I_2, [18]-crown-6, CH_2Cl_2, reflux, 80%; d) CAN, ACN/H_2O (2.5:1), 90%; e) Jones reagent, acetone, –78 °C to r.t.; f) DCC, DMAP, **3.38,** THF, r.t., 70% (over two steps); g) LDA, TMSCl, THF, –78 °C to r.t. to reflux; h) TsOH x H_2O, MeOH, reflux, 54% (over two steps), *d.r.* = 7:1; i) Ph_3CBF_4, CH_2Cl_2, reflux, 60%; j) TBSOTf, Et_3N, CH_2Cl_2, r.t., 85%; k) [$Co_2(CO)_8$], Bu_3PS, toluene, r.t. to 75 °C, 67%; l) hν, allene, THF, –78 °C, 87%, *d.r.* = 4.8:1; m) O_3, MeOH, CH_2Cl_2; Me_2S, –78 °C to r.t.; NaOMe, MeOH, 89%; n) LDA, TMSCl, Et_3N, THF, –78 °C to –20 °C; o) $Pd(OAc)_2$, O_2, DMSO, 75 °C, 92% (over two steps); p) TBAF, THF, r.t., 96%; q) NaHMDS, (–)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine, THF, –78 °C, 55%; r) Jones reagent, acetone, 0 °C; MeOH, r.t., 46%.

3.2.3 Fukuyama's Enantioselective Formal Synthesis of (–)-Jiadifenin

Fukuyama reported a formal synthesis of (–)-jiadifenin (**3.11**) in 2015 in 30 steps and an overall yield of 0.09% (Scheme 3.4).[185] The key step involved a tandem Tsuji-Trost and an intramolecular Mizoroki-Heck reaction. Diethyl-4-oxopimelate (**3.44**) was subjected to a Wittig reaction to yield the trisubstituted olefin, followed by a global ester reduction and mono-alcohol protection to afford the desymmetrized product **3.45**. The free alcohol was oxidized under Swern conditions to the aldehyde and a HWE-reaction afforded the unsaturated ester **3.46**. The cyclization took place under a Pd-catalyzed, intramolecular Mizoroki-Heck reaction to afford the cyclized product **3.47**. The olefin was first hydroborated and the obtained alcohol was protected with triethylsilane. The installation of the α–hydroxyketone function was achieved after conversion of the ester to the Weinreb amide and treatment with MeMgBr to afford the ketone. A Rubottom-oxidation furnished the desired α-hydroxyketone **3.48**. The ketone was then treated with MeLi and the diol was transformed into the carbonate. An acidic cleavage of the TES-group and oxidation of the alcohol to the aldehyde was directly subjected to a Roskamp reaction with ethyl diazoacetate to furnish the β-ketoester **3.49**. A tandem Tsuji-Trost reaction furnished the ABC-ring system **3.50** after and extensive condition and ligand screening. The olefin was installed after silyl deprotection and a Grieco dehydration. The hydroxy group was introduced with *m*-CPBA to yield the α-hydroxyester **3.51**. The olefin was converted into the aldehyde under Johnson-Lemieux conditions and formed the lactol spontaneously, which was oxidized to Theodorakis lactone intermediate **3.52** using Fetizon's reagent. The data were in good agreement with those reported by the Theodorakis group.[186]

[185] K. Harada, A. Imai, K. Uto, R. G. Carter, M. Kubo, H. Hioli, Y. Fukuyama, *Tetrahedron* **2015**, *71*, 2199.

[186] L. Trzoss, J. Xu, M. H. Lacoske, W. C. Mobely, E. A. Theodorakis, *Org. Lett*. **2011**, *13*, 4554.



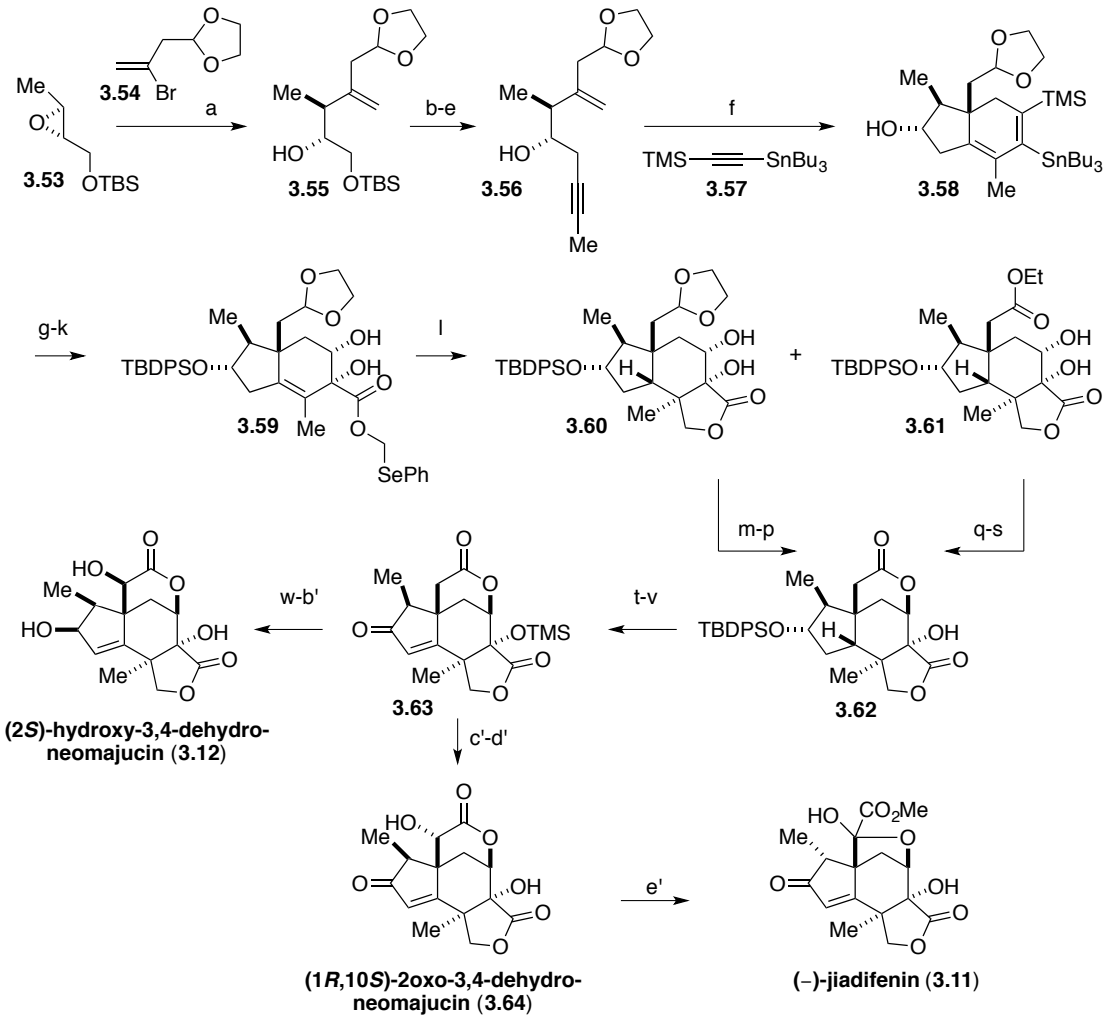
Scheme 3.4: Fukuyama's formal synthesis of (–)-jiadifenin (**3.11**). a) $EtPPh_3Cl$, *n*-BuOK, toluene, 81%; b) $LiAlH_4$, THF, 81%; c) TPDPSCl, imid., CH_2Cl_2, 56%; (d) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N; e) $(EtO)_2P(O)CH_2CO_2Et$, NaH, DME, Br_2, KHMDS, 70% (over two steps); f) $Pd(OAc)_2$, (*o*-tol)$_3$P, Et_3N, *t*-BuOH, 99%; g) TMSOK, Et_2O, 98%; h) MeNHOMe, EDC, CH_2Cl_2, 85%; i) 9-BBN, THF, NaOH, H_2O, 78%; j) TESCl, Et_3N, DMAP, CH_2Cl_2, 98%; k) MeMgBr, THF, 76%; l) TMSCl, LDA, THF; m) *m*-CPBA, CH_2Cl_2, K_2CO_3, 78% (over two steps); n) MeLi, THF (*d.r.* = 1:1); o) CDI, DMAP, CH_2Cl_2, 89% (over two steps); p) AcOH, H_2O, THF, 88%; q) DMAP, CH_2Cl_2, 99%; r) $SnCl_2$, N_2CHCO_2Et, CH_2Cl_2, 83%; s) $Pd(OAc)_2$, LiOAc, (±)-BINAP, *t*-BuOH, 65%; t) TBAF, THF, 94%; u) $NCSeC_6H_4NO_2$, PPh_3, py, 52%; v) H_2O_2, 97% (over three steps); w) *m*-CPBA, CH_2Cl_2, 86%; x) $NaBH_4$, MeOH, 99%; y) OsO_4, $NaIO_4$, THF, H_2O, 54%; z) Ag_2CO_3, CH_2Cl_2, 92%.

3.2.4 Micalizio's Enantioselective Total Synthesis of (–)-Jiadifenin

The Micalizio group published a novel approach for the synthesis of (–)-jiadifenin in 21 steps (Scheme 3.5).[187] The report highlights a hydroxy-directed, metallacycle-mediated [2 + 2 + 2] annulation and an intramolecular radical cyclization cascade. Starting from the chiral epoxide **3.53**, and addition of the organometallic derived vinylbromide **3.54** furnished the secondary alcohol **3.55**. The enyne **3.56** was obtained from a desilylation, epoxide formation and opening with propynyl lithium. Cyclization in the presence of $Ti(O^iPr)_4$ and a stannyl-substituted TMS-acetylene **3.57** furnished the

[187] X. Chen, G. C. Micalizio, *J. Am. Chem. Soc*. **2016**, *138*, 1150.

[2 + 2 + 2] annulated product **3.58**. The TMS-group was removed and the secondary alcohol TBDPS-protected. A tin-lithium exchange was performed and subsequent carboxylation followed by an esterification reaction gave the ester moiety. A dihydroxylation of the olefin furnished the precursor **3.59**. The radical cyclization furnished the desired lactone **3.60**, as well the unexpected ethyl ester **3.61**, which might arise from a reaction of the tertiary radical with the acetal group, followed by acetal opening to the ethyl ester **3.61**. Nevertheless, both compounds could be successfully converted in the lactone **3.62** *via* a reduction and oxidation sequence. The A-ring was further modified by TBDPS-cleavage, oxidation of the secondary alcohol and a Saeguesa-Ito oxidation yielded in the enone **3.63**. Out of this intermediate, the total synthesis of (2*S*)-3,4-dehydroneomajucin (**3.12**), (1*R*,10*S*)-2-oxo-3,4-dehydroneomajucin (**3.64**) and (–)-jiadifenin (**3.11**) could be accomplished.



Scheme 3.5: Micalizio's total synthesis of (–)-jiadifenin (**3.11**). a) Mg, CuI, THF, 59% b) TBAF, THF, 81%; c) TsCl, Et_3N, DMAP, CH_2Cl_2 (92%); d) NaH, THF, 76%; e) propynyl

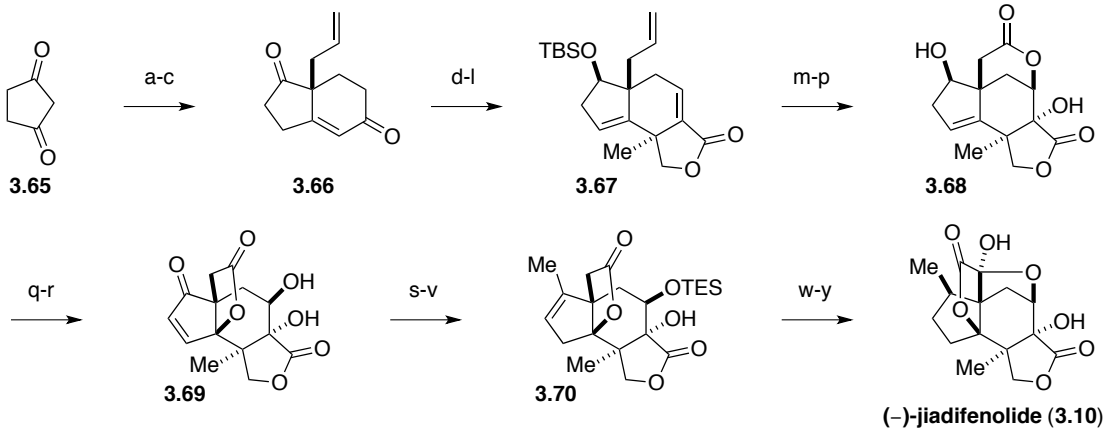
lithium, BF_3 x OEt_2, 91%; f) $Ti(O^iPr)_4$, *n*-BuLi, PhMe, –78 °C to 50 °C, then PhCHO, 73%; g) TBAF, DMSO, 65%; h) TBDPSCl, imid., CH_2Cl_2, 96%; i) MeLi, THF, then CO_2; j) $PhSeCH_2Cl$, $^iPr_2NEt$, NaI, DME, 50% (over two steps); k) OsO_4, pyridine, THF, 85%; l) Bu_3SnH, AIBN, PhH, 80 °C, 80%; m) $(COCl)_2$, DMSO, Et_3N, 71%; n) HCl, THF, 85%; o) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4; p) $NaBH_4$, then TsOH, toluene, 70% (over three steps); q) $(COCl)_2$, DMSO, Et_3N, 80%; r) $NaBH_4$, MeOH, 97%; s) TsOH, PhMe, 86%; t) TBAF, THF, 87%; u) IBX, DMSO 97%; v) LDA, TMSCl, then $Pd(OAc)_2$, 83%; w) $NaBH_4$, $CeCl_3$ x 7 H_2O, MeOH, 92%; x) NaHMDS, THF, 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine, 50%; y) PPh_3, DIAD, *p*-NO_2-benzoic acid; z) DMP; a') $NaBH_4$; b') K_2CO_3, MeOH, 14% (over four steps); c') TBAF, THF, 70%; d') NaHMDS, THF, 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine, 54%; e') Jones reagent, acetone, 0 °C; MeOH, r.t., 46%.

3.2.5 Theodorakis' Enantioselective Synthesis of (–)-Jiadifenolide

The group of Theodorakis was the first to accomplish the enantioselective total synthesis of (–)-jiadifenolide (**3.10**) in 2011 (Scheme 3.6).[188] Starting from diketone **3.65**, a dialkylation was performed to the optically enriched diketone (>90% *ee*), which was prone to a D-prolinamide/PPTS-catalyzed asymmetric aldol condensation to furnish the AB-ring system **3.66**. A carboxylation of the C-5 enolate and trapping of the carboxylic acid with Meerwein's salt furnished the ethylester. Methyl insertion was achieved by formation of the silyl enol ether and subsequent silyl deprotection with TBAF/MeI furnished the α-methylated product as a single diastereomer. The installation of the C-ring was achieved by a global carbonyl reduction, silyl protection of the primary alcohol and oxidation of the secondary alcohol to the ketone. The ketone was transformed into the vinyltriflate, which was converted to the methylester *via* a Pd^0-catalyzed carbomethoxylation and finally TBS-deprotection yielded directly in the lactone **3.67**. The α,β-unsaturated lactone was epoxidized and the terminal olefin was subjected to Johnson-Lemieux conditions. The aldehyde was oxidized under Jones conditions to the carboxylic acid, which triggered a "6-*exo*-*tet*" epoxide opening to the lactone. A TBS-deprotection led to the free alcohol **3.68**. Epoxidation of the trisubstitued olefin occurred from the β-face and epoxide opening was achieved in the presence of DMP to the translactonized product

[188] J. Xu, L. Trzoss, W. K. Chang, E. A. Theodorakis, *Angew. Chem. Int. Ed*. **2011**, *50*, 3672.

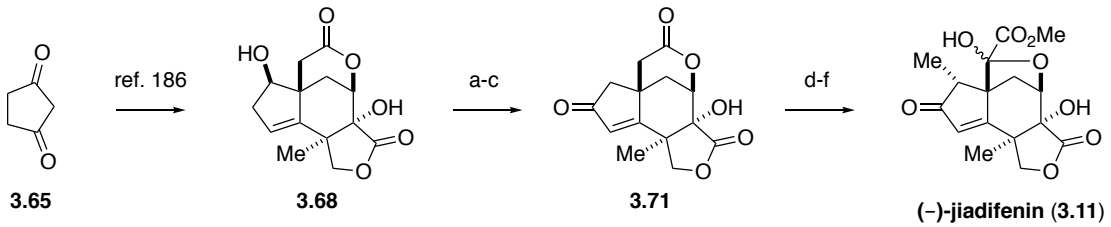
3.69. The authors claimed that the released acid protonates the epoxide and opens it *via* an elimination reaction. Hydrogenation of the obtained double bond and TES-protection of the alcohol and then the ketone was readily converted into the vinyltriflate with Comins reagent, followed by a Pd^0-mediated cross-coupling using $AlMe_3$ to furnish compound **3.70**. The trisubstitued olefin was selectively hydrogenated from the β-face and the final assembly was achieved by applying Danishefsky's conditions.[183] Therefore, (–)-jiadifenolide (**3.10**) was enantioselective synthesized in 25 linear steps in 0.5% overall yield from the commercially available diketone **3.65**.



Scheme 3.6: Theodorakis' enantioselective synthesis of (–)-jiadifenolide (**3.10**). a) allyl acetate, $[PdC_3H_5Cl_2]_2$, BSA, cat. NaOAc, THF, reflux 24 h, 90%; b) methyl vinyl ketone, H_2O, r.t., 54%; c) D-prolinamide (30 mol %), PPTS (30 mol %), MeCN, 40 °C, 14 d, 74% (>90% *ee*); d) $NaBH_4$ (0.25 eq.), EtOH, 0 °C, 1 h; e) TBSCl, NH_4NO_3, DMF, r.t., 12 h, 92% (over two steps); f) MMC, DMF, 130 °C, 3 h; Et_3OBF_4, $^iPr_2NEt$, CH_2Cl_2, 0 °C, 5 min; g) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to r.t., 1 h; TBAF (1.0 eq.), MeI, THF, –78 °C to r.t., 3 h, 43% (over two steps); h) $LiAlH_4$, THF, 0 °C to r.t., 1 h; i) TBSCl (1.0 eq.), imid., CH_2Cl_2, 0 °C, 30 min; j) IBX, DMSO, 80 °C, 1 h, 85% (over three steps); k) KHMDS, $PhNTf_2$, THF, –78 °C, 1 h; l) CO (1 atm), $[Pd(PPh_3)_4]$ (1 mol%), MeOH, DMF, Et_3N, 50 °C, 2 h; TFA, CH_2Cl_2, r.t., 5 h, 69% (over two steps); m) H_2O_2, 3 M NaOH, THF, 0 °C to r.t., 5 h, 99%; n) OsO_4 (1 mol%), $NaIO_4$, 1,4-dioxane, H_2O, r.t., 12 h; o) Jones reagent, acetone, 0 °C, 30 min, 70% (over two steps); p) TBAF, THF, r.t., 30 min, 95%; q) *m*-CPBA, THF, 50 °C, 3 h; r) DMP, acetone, r.t., 2h, 38%, (over two steps); s) H_2, 10% Pd/C (5 mol%), MeOH, r.t., 24 h; t) TESOTf, 2,6-lutidine, THF, 0 °C to r.t., 30 min, 90%, (over two steps); u) KHMDS, Comins reagent, THF, –78 °C, 1.5 h; v) $AlMe_3$, $[Pd(PPh_3)_4]$ (50 mol%), THF, r.t., 2 h, 57%, (over two steps); w) H_2 (90 atm), PtO_2 (20 mol%), MeOH, r.t., 24 h; x) NaHMDS, (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine, THF, –78 °C to r.t., 1.5 h; y) Jones reagent, acetone, 0 °C, 15 min, 33%, (over three steps).

3.2.6 Theodorakis' Enantioselective Synthesis of (–)-Jiadifenin

The first enantioselective synthesis of (–)-jiadifenin (**3.11**) was reported shortly after the accomplishment of (–)-jiadifenolide (**3.10**) by the same group (Scheme 3.7).[186] Slight modifications of the endgame furnished (–)-jiadifenin (**3.11**) in 19 linear steps and an overall yield of 1.1% starting from the diketone **3.65**. The hydroxy-intermediate **3.68** was dehydrated using Martin's sulfurane and the alkene selectively hydrogenated to the mono-alkene, which was oxidized in allylic position to the enone **3.71**. α-Hydroxylation of the lactone moiety and α-methylation yielded the known precursor for Jones oxidation and finally the enantioselective synthesis of (–)-jiadifenin (**3.11**) was accomplished.



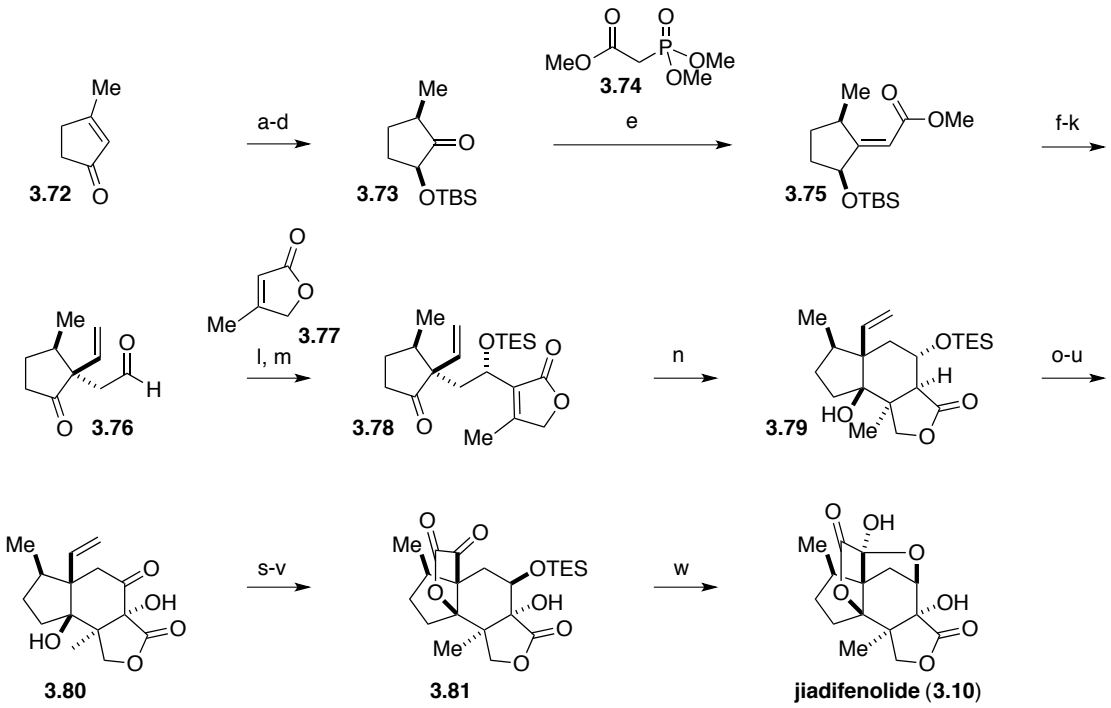
Scheme 3.7: Theodorakis' enantioselective synthesis of (–)-jiadifenin (**3.11**). a) Martin's sulfurane, THF, r.t., 2 h; b) H_2, Pd/C, MeOH, r.t., 1 h, 72%, (over two steps); c) $Mn_3O(OAc)_9$, *t*-BuOOH, EtOAc, 3Å molecular sieve, 40 °C, 16 h, 65%; d) NaHMDS, Davis' oxaziridine, THF, –78 °C, 1 h, 61%; e) LDA, MeI, THF, HMPA, –78 °C to –10 °C, 4 h, 60% brsm; f) Jones reagent, acetone, r.t., 20 min; MeOH, r.t., 15 min, 45%.

3.2.7 Paterson's Total Synthesis of (±)-Jiadifenolide

Paterson and co-workers reported a new synthetic approach for the synthesis of (±)-jiadifenolide (**3.10**) in 23 linear steps and an overall yield of 2.3% (Scheme 3.8).[189] Commercially available enone **3.72**, representing the A-ring, was converted in four steps to the cyclopentanone **3.73**. A HWE-homologation with phosphonate ester **3.74** afforded the α,β-unsaturated ester **3.75**. After reduction and acetylation, an Ireland-Claisen-rearrangement afforded the quaternary C-9 with the desired stereochemistry. An ester reduction to the alcohol, followed by a TBS deprotection and oxidation

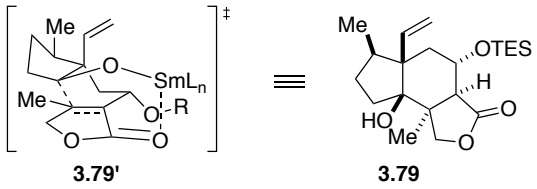
[189] I. Paterson, M. Xuan, S. M. Dalby, *Angew. Chem. Int. Ed*. **2014**, *53*, 7286.

afforded the aldehyde **3.76**. A boron-mediated aldol reaction with butenolide **3.77** introduced the C-ring, which gave **3.78** after TES protection.



Scheme 3.8: Paterson's synthesis of (±)-jiadifenolide (**3.10**). a) $NaBH_4$, $CeCl_3$, MeOH, –78 °C to 0 °C; b) *m*-CPBA, CH_2Cl_2, 0 °C; c) TBSCl, imid., CH_2Cl_2 0 °C to r.t., 65 % (over three steps); d) BF_3 x OEt_2, CH_2Cl_2, –20 °C, 78%; e) NaH, r.t., 72 h, 73%; f) $LiAlH_4$, Et_2O, 0 °C; g) Ac_2O, py, DMAP, CH_2Cl_2, r.t., 77% (over two steps); h) LDA, TBSCl, THF, –78 °C to r.t.; toluene, reflux, 16 h; i) $LiAlH_4$, Et_2O, 0 °C, 63% (over two steps); j) 3 M HCl, MeOH, (1:3), r.t.; k) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, –78 °C to r.t., 74% (over two steps); l) Bu_2BOTf, $^{i}Pr_2NEt$, THF, –78 °C to –20 °C, 98%, *d.r.* = 2:1; m) TESCl, imid., DMF, r.t., 65%; n) SmI_2, 65 °C, 2 h, 51%; o) *p*-TsOH, MeOH, CH_2Cl_2, r.t., 88%; p) PCC, NaOAc, SiO_2, CH_2Cl_2, 81%; q) TMSOTf, Et_3N, THF, –78 °C; r) OsO_4, NMO, *t*-BuOH/H_2O, r.t., 99% (over two steps); s) $Me_4NBH(OAc)_3$, AcOH, MeCN, –20 °C, 87%; t) TESCl, imid., DMF, r.t., 96%; u) OsO_4, NMO, py, *t*-BuOH/H_2O, r.t.; v) TPAP, NMO, 4Å molecular sieve, CH_2Cl_2, r.t., 84% (over two steps); w) HF · py, THF, r.t., 86%.

The formation of the B-ring was achieved by a samarium-mediated cyclization as the key step. Figure 3.9 shows the proposed transition state **3.79'** of the cyclization in which the coordination of the samarium led to a boat conformation and to the desired diastereomer **3.79**.



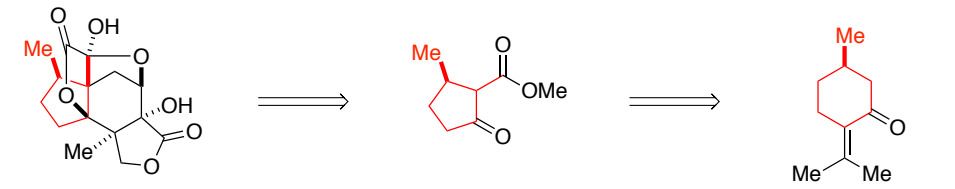
3.79' **3.79**

Figure 3.9: Proposed radical cyclization transition state **3.79'** to ABC ring system **3.79**.[189]

After TES deprotection and oxidation of the secondary alcohol, the β-ketolactone was α-hydroxylated at C-6 to insert the last oxygen on the C-ring and to yield ketone **3.80**. The terminal alkene was dihydroxylated, followed by a TPAP oxidation to form the ketoaldehyde (E-ring), which was subsequently converted to the ketolactone **3.81**. The D-ring is then formed by an intramolecular nucleophilic attack of the C-7 alcohol to the α-ketolactone, completing the synthesis of (±)-jiadifenolide (**3.10**).

3.2.8 Sorensen's Enantiospecific Synthesis of (–)-Jiadifenolide

The group of Sorensen reported on the enantioselective total synthesis of (–)-jiadifenolide (**3.10**) in 21 steps and an overall yield of 0.5%.[190] They employed a similar "pattern recognition" (Scheme 3.9) as described by Danishefsky for their synthesis. β-Ketoester **3.82**, which was synthesized from enantiopure (*R*)-pulegone (**3.83**), was found to be an ideal starting material for the synthesis. It bears already seven carbons of the natural product (–)-jiadifenolide (**3.10**) with the correct configuration of the methyl group.

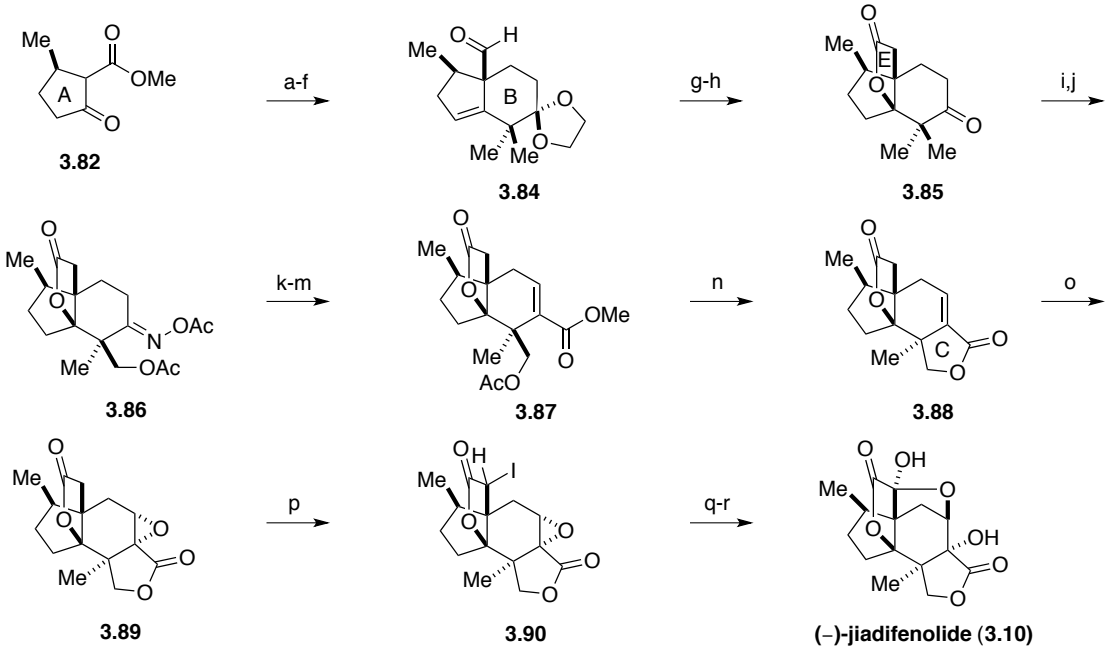


(–)-jiadifenolide (3.10) **3.82** **(*R*)-pulegone (3.83)**

Scheme 3.9: (*R*)-Pulegone (**3.83**), β-ketoester **3.82** and (–)-jiadifenolide (**3.10**) with "pattern recognition" (shown in red).

[190] D. A. Siler, J. D. Mighion, E. J. Sorensen, *Angew. Chem. Int. Ed*. **2014**, *53*, 5332.

A Michael addition of methyl vinyl ketone on to β-ketoester (**3.82**), followed by a Robinson annulation furnished the AB-ring system (Scheme 3.10). After methylation on C-5 and acetal formation, the ester was reduced to the alcohol and then oxidized by Swern method to afford the aldehyde **3.84**. A van Leusen homologation was used to afford the nitrile and upon hydrolysis, the ABE-lactone-ring system **3.85** was formed. Oxidation of the geminal methyl group was achieved by using Sanford's oxime directed C-H activation to afford **3.86**. Both methyl groups were hydroacetylated in a 1:1 ratio. After reductive cleavage of the oxime acetate, Comins's reagent furnished the enol triflate, which could be converted into the methyl ester **3.87** in a palladium-catalyzed carbomethoxylation. After deprotection of the acetate, the bislactone **3.88** was obtained. Epoxidation of the α-unsaturated-bislactone **3.88** afforded the epoxide **3.89**. Halogenation of the E-ring afforded the α-iodolactone **3.90**. Oxidation with dimethyldioxirane yielded in the α-ketolactone, which was treated with LiOH to afford (–)-jiadifenolide (**3.10**).



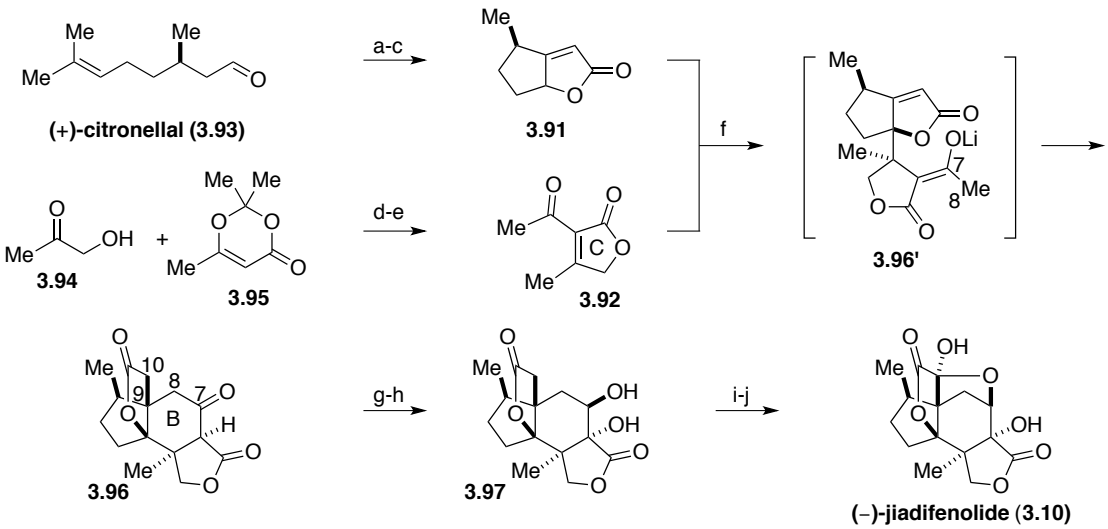
Scheme 3.10: Enantiospecific total synthesis of (–)-jiadifenolide (**3.10**) by the Sorensen group. a) methyl vinyl ketone, DBU, EtOH, r.t., 97%; b) *p*-TsOH, benzene, reflux, 85%; c) CH_3I, KO*t*-Bu, *t*-BuOH, r.t., 91%; d) ethylene glycol, *p*-TsOH, benzene, reflux; e) DIBAL-H, CH_2Cl_2, –78 °C to 0 °C, 77% (over two steps); f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C to r.t., 90%; g) TosMIC, KO*t*-Bu, THF, –50 °C, CH_3OH, 65 °C, 90%; h) H_2SO_4, MeOH, 100 °C, 73%; i) $HONH_2 \cdot HCl$, py, 80 °C, 91%; j) $Pd(OAc)_2$, $PhI(OAc)_2$, Ac_2O/AcOH (1:1), 100 °C, 12 h, 22%; k) Fe, AcOH, TMSCl, THF, r.t., 89%; l) KHMDS, Comins reagent, THF, –78 °C; m) $Pd(OAc)_2$, PPh_3, Et_3N, CO (1 atm), MeOH, DMF, 40 °C, 49% (over two steps); n) K_2CO_3,

CH_3OH, r.t.; o) 3 M NaOH, H_2O_2, MeOH, 0 °C to r.t., 61% (over two steps); p) TMSCl, LiHMDS, THF, –78 °C, NIS; q) DMDO, acetone, CH_2Cl_2, r.t.; r) LiOH, THF, r.t., 40% (over three steps).

3.2.9 Shenvi's Eight-Step Gram-Scale Synthesis of (–)-Jiadifenolide

Shenvi and co-workers demonstrated a straightforward eight-step synthesis of (–)-jiadifenolide (**3.10**) in an overall yield of 9.2% (Scheme 3.11).[191] They used a convergent synthetic approach based on two main fragments **3.91** and **3.92**, which are connected in a double Michael addition. The chiral butenolide fragment **3.91** was synthesized with a new synthetic strategy using (+)-citronellal (**3.93**) as a chiral starting material. Dehydration of the aldehyde afforded the alkyne and ozonolysis of the alkene furnished the corresponding aldehyde. A hetero-Pauson-Khand reaction using molybdenum hexacarbonyl and TBAB yielded in the butenolide **3.91**, which already represents the AE-ring system of the natural product. Thermolysis of hydroxyacetone **3.94** and dioxinone **3.95** yielded into a linear β-ketoester, which cyclized to the acetyl butenolide **3.92**, upon treatment with silica. The key step, a double Michael addition, led to the β-ketolactone **3.96**. To prevent a [4 + 2] cycloaddition *via* intermediate **3.96'**, $Ti(O^iPr)_4$ showed to be superior over other tested Lewis acids. The resulting β-ketolactone **3.96** was α-hydroxylated using *m*-CPBA and the ketone was reduced to yield the anti-diol **3.97.** A α-bromination on the E-ring lactone furnished α-bromolactone, which was treated with Davis' oxaziridine to afford (–)-jiadifenolide (**3.10**).

[191] H.-H. Lu, M. D. Martinez, R. A. Shenvi, *Nature Chemistry* **2015**, *7*, 604.

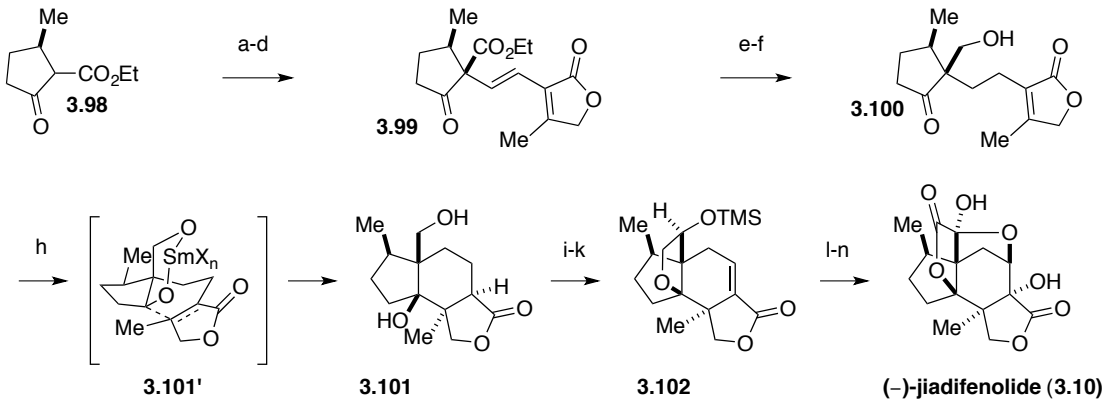


Scheme 3.11: Shenvi's gram-scale synthesis of (–)-jiadifenolide (**3.10**)**.** a) BTPP, NfF, 22 °C; b) O_3, CH_2Cl_2, –78°C; c) $Mo(CO)_6$, Bu_4NBr, CH_2ClCH_2Cl, 90 °C, 35% (over three steps); d) hydroxyacetone, PhMe, 120 °C; e) SiO_2, 22 °C, EtOAc, C_6H_{14}, 45% (over two steps); f) LDA, **3.91**, THF, –78 °C, **3.92**, –100 °C, then $Ti(O^iPr)_4$, LDA, 0 °C, 70%; g) *m*-CPBA, CH_2Cl_2, r.t.; h) $Me_4NBH(OAc)_3$, AcOH, THF, 75% (over two steps); i) LDA, CBr_4; j) NaHMDS, Davis's oxaziridine, 50% (over two steps).

3.2.10 Zhang's Protecting-Group-Free Total Synthesis of (–)-Jiadifenolide

Recently, Zhang and co-workers reported on a protecting-group-free total synthesis of (–)-jiadifenolide (**3.10**).[192] The β-ketoester **3.98** was readily converted into the unsaturated butenolide **3.99** in four steps (Scheme 3.12). After ester reduction and olefin hydrogenation, the key cyclization using SmI_2 with alcohol **3.100** gave the ABC-structure **3.101**. The authors proposed a chelating effect of SmI_2 to the alcohol and ketone function (**3.101'**), resulting in a diastereomeric ratio of 7:1. C1-homologation was achieved *via* a formal [4 + 1] annulation reaction using with $TMSCHN_2$ to form ether **3.102**. Finally, several oxidation steps and a basic treatment furnished (–)-jiadifenolide (**3.10**) in 13 steps and an overall yield of 7.9% starting from the β-ketoester **3.98**.

[192] Y. Shen, L. Li, Z. Pan, Y. Wang, J. Li, K. Wang, X. Wang, Y. Zhang, T. Hu, Y. Zhang, *Org. Lett*. **2015**, *17*, 5480.



Scheme 3.12: Zhang's protecting-group-free total synthesis of (–)-jiadifenolide (**3.10**). a) allylbromide, Cs_2CO_3, acetone, 0 °C, 99%; b) O_3, CH_2Cl_2, –78 °C then PPh_3, 92%; c) 4-methylfuran-2(5*H*)-one, Et_3N, Bu_2BOTf, CH_2Cl_2, –78 °C, 84%; d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 85%; e) LDA, THF, DIBAL-H, –78 °C, 78%; f) PtO_2, H_2, EtOAc, 85%; h) SmI_2, THF/H_2O, 89%, *d.r.* = 7:1; i) DMSO, oxalyl chloride, Et_3N, CH_2Cl_2, –78 °C, quant.; j) $TMSCHN_2$, *n*-BuLi, LiCl, THF, –78 °C, 78%; k) KHMDS, PhSeBr, THF, –78 °C, then H_2O_2 or *m*-CPBA, 70-88%; l) DMDO, Na_2SO_4, 80%; m) $RuCl_3$, $NaIO_4$, CCl_4, ACN, H_2O, 84%; n) LiOH, THF, H_2O, 71%.

3.2.11 Synthetic Investigations and SAR-Studies on *Nor*-Sesquiterpenoids

Intensive SAR-studies contributed by Danishefsky[193] and Theodorakis[194] on majucin type sesquiterpene structures gave an insight into the recommended structural features for neurotrophic properties as shown in Table 3.1. Modifications on the A-ring did not show an increased neurotrophic activity (**3.103a-c**). The α-substituents of the bridged E-ring lactone showed to be the important structural motif for neurotrophic activity (**3.104a-d**). This was further expanded to methyl (**3.104d**) and hydroxy substitution (**3.104b-c**) pattern, whereas only the α-configuration (**3.104c**) showed an increased activity. This is as well the case for a α-methyl substituent (**3.104d**), which indicates that the orientation at this position and less the substituent is inducing neurite outgrowth properties.

[193] D. A. Carache, Y. S. Cho, Z. Hua, Y. Tian, Y.-M. Li, S. J. Danishefsky, *J. Am. Chem. Soc.* **2006**, *128*, 1016.

[194] L. Trzoss, J. Xu, M. H. Lacoske, W. C. Mobley, E. A. Theodorakis, *Chem. Eur. J.* **2013**, *19*, 6398.

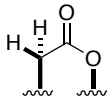
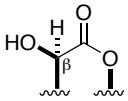
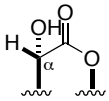
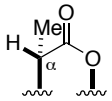
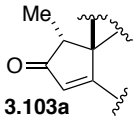
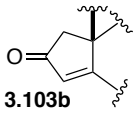
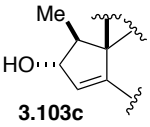
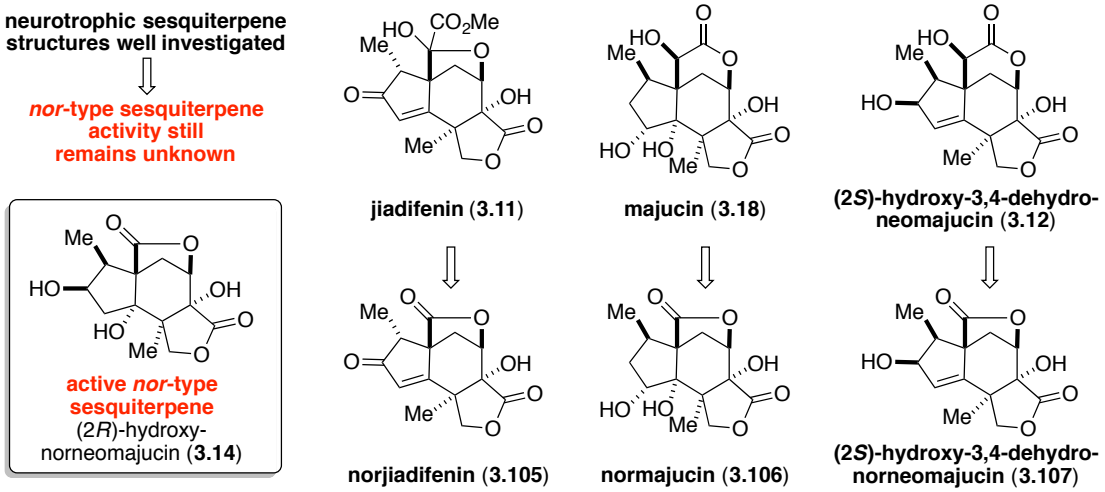
	 **3.104a**	 **3.104b**	 **3.104c**	 **3.104d**
 **3.103a**	inactive	inactive	active	active
 **3.103b**	inactive	–	active	active
 **3.103c**	inactive	inactive	active	–

Table 3.1: Structural activity profile (inactive = less or similar neurotrophic activity; active = increased neurotrophic activity; – = structure not accessible)

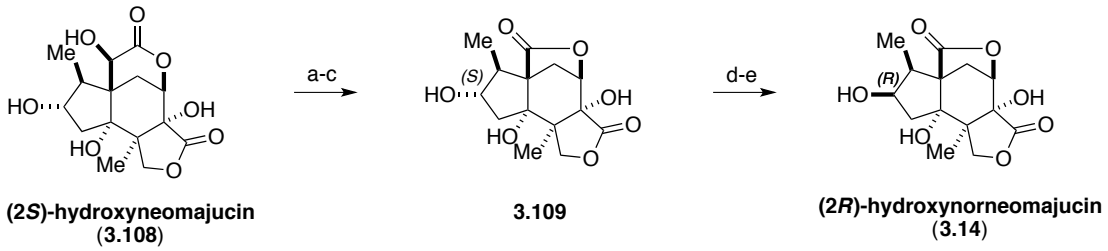
However, this in contrast to other neurotrophic *nor*-type sesquiterpens which are lacking the C-10 carbon. One of the most active *nor*-type molecules is (2*R*)-hydroxynorneomajucin (**3.14**), which consists of a carbonyl function at the C-10 carbon. A synthetic approach to the *nor*-type sesquiterpene scaffold should provide an access to a novel neurotrophic activity map. Furthermore, *nor*-type structure (**3.105** - **3.107**) of active natural products such as jiadifenin (**3.11**), majucin (**3.18**) and (2*S*)-hydroxy-3,4-dehydro-neomajucin (**3.12**) could be tested on their neurotrophic behavior as shown in Scheme 3.13.



Scheme 3.13: Neurotropic activity development program on uninvestigated *nor*-type sesquiterpene natural products.

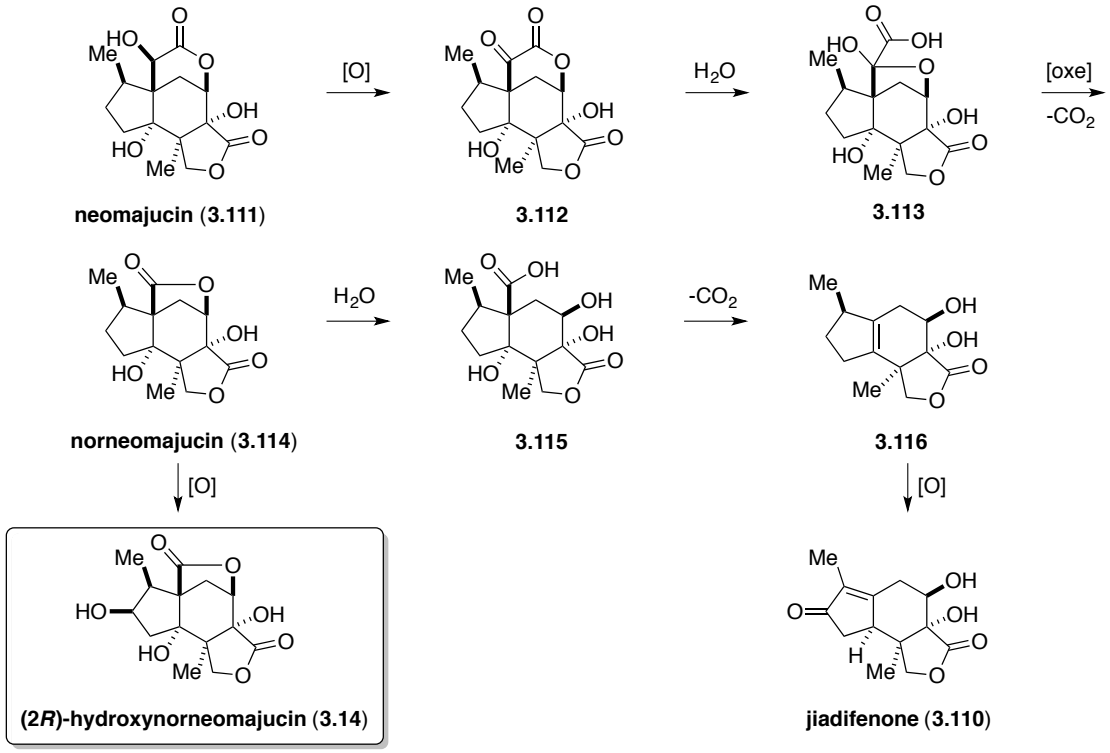
3.2.12 Structural Elucidation of *Nor*-Sesquiterpenoid (2*R*)-Hydroxynorneomajucin

Our main interest was in the highly active neurite promoter (2*R*)-hydroxynorneomajucin (**3.14**), which was isolated in 2012 by Fukuyama and co-workers from a methanol extract of the pericarps of *Illicium jiadifengpi*.[181] It has remarkable activity in primary cultured rat cortical neurons with an activity range of 1 – 10 μM. The structure was elucidated *via* chemical modifications (Scheme 3.14) from (2*S*)-hydroxyneomajucin (**3.108**) *via* degradation to the norsesquiterpenoid **3.109**. The secondary (*S*)-configured alcohol at C-2 was oxidized to the ketone and reduced to yield in a (*R*)-configured alcohol at C-2. The spectroscopic data were identical with the natural occurring (2*R*)-hydroxynorneomajucin (**3.14**)



Scheme 3.14: Structural elucidation of (2*R*)-hydroxynorneomajucin (**3.14**) *via* chemical transformation. a) Ac_2O, py, 99%; b) Jones reagent, acetone, 15%; c) K_2CO_3, MeOH, 99%; d) IBX, DMF, 66%; e) $NaBH_4$, MeOH, 99%.

Along with the structure elucidation of (2*R*)-hydroxynorneomajucin (**3.14**), a second inactive metabolite was isolated named jiadifenone (**3.110**). From this data, the authors proposed a biosynthesis for both compounds as depicted in Scheme 3.15. Neomajucin (**3.111**) is oxidized to the strained α-keto-δ-lactone **3.112**, which opens to the α-keto-carboxylic acid **3.113**. An enzymatic oxidation leads to a decarboxylation and norneomajucin (**3.114**) is formed. Further oxidation at C-2 forms (2*R*)-hydroxynorneomajucin (**3.14**), whereas a hydrolysis opens the lactone moiety to yield the carboxylic acid **3.115**, which decarboxylates and eliminates to the jiadifenone precursor **3.116**. Oxidation at C-2 furnishes jiadifenone (**3.110**).



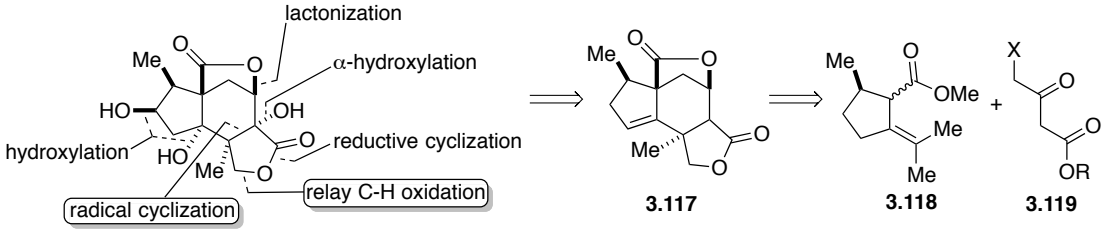
Scheme 3.15: Proposed biosynthesis of (2*R*)-hydroxynorneomajucin (**3.14**) and jiadifenone (**3.110**).

3.3 Goal of this Study and Retrosynthetic Analysis of (2*R*)-Hydroxynorneomajucin

The goal of this project is to elucidate the neurite outgrowth inducing potential of *nor*-sesquiterpenoids. In a first step, a general synthetic pathway should be established, which targets a common advanced intermediate for further transformation and substitution to cover a broad spectra of *nor*-type related natural products. In a second step, the molecules should be tested on their neurite outgrowth potential. The synthetic aspects are shared with M.Sc. Joel Rösslein, who contributed ideas and synthetic effort on this project.

The synthetic overview for the total synthesis of (2*R*)-hydroxynorneomajucin (**3.14**) is summarized in Scheme 3.16. The hydroxylation events should take place at late stage *via* α-hydroxylation, allylic oxidation and epoxidation. This precursor **3.117** would allow further transformation to a broad spectra of *nor*-type sesquiterpenes. Formation of the B-ring will be accessed *via* a radical cyclization between a α,β-ketoester

radical and a tetrasubstitued olefin. A hydroxy directed relay C-H activation will stereospecifically introduce a hydroxy function on the geminal methyl functions, which is further used in the reductive cyclization to form the C-ring lactone. As a starting material the known methylester **3.118** from commercially available (*R*)-pulegone (**3.83**) and a β-ketoester **3.119** would be used.



Scheme 3.16: Retrosynthetic analysis of (2*R*)-hydroxynorneomajucin (**3.14**).

3.3.1 Synthetic Plan

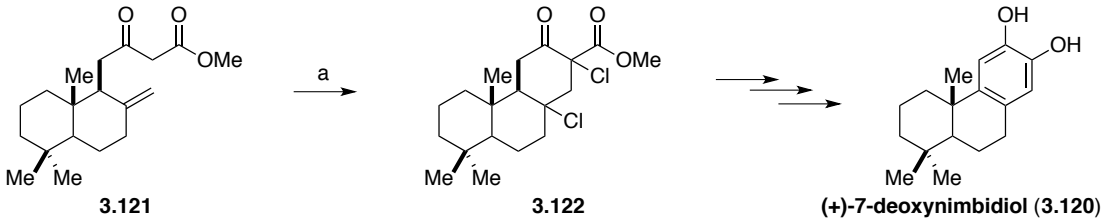
The two challenging steps in the synthesis are the assembly of the B- and C-ring *via* a planned radical cyclization and relay C-H oxidation (highlighted in Scheme 3.16). The methodology is discussed with literature known examples in this section.

We could recently demonstrate[195] that six-ring formation can be achieved *via* a manganese(III)-mediated cross coupling[196] onto an internal olefin (the reaction is described in full detail in chapter four of this thesis). An oxygen free radical cyclization was used in the work of Alvarez and co-workers for their total synthesis of (+)-7-deoxynimbidiol (**3.120**, Scheme 3.17). A radical cyclization of the β-ketoester **3.121** formed the bis-chlorinated 6-ring **3.122**. The chlorines were easily removed by a treatment with base.[197]

[195] C. Daeppen, M. Kaiser, M. Neuburger, K. Gademann, *Org. Lett*. **2015**, *17*, 5420.

[196] B. B. Snider, *Chem. Rev.* **1996**, *96*, 339; *Tetrahedron* **2009**, *65*, 10738.

[197] E. Alvarez-Manzaneda, R. Chahboun, E. Cabrera, E. Alvarez, R. Alvarez-Manzaneda, M. Hmamouchi, H. Es-Samti, *Tetrahedron Lett.* **2007**, *48*, 8930.

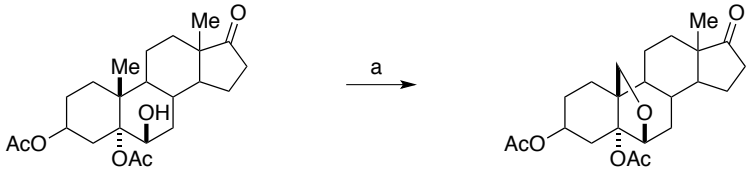


3.121 **3.122** **(+)-7-deoxynimbidiol** (**3.120**)

Scheme 3.17: Synthesis of (+)-7-deoxynimbidiol (**3.120**) with a Mn(III)-mediated cyclization as the key step**.** a) $Mn(OAc)_3$ x 2 H_2O (4.0 eq.), LiCl (3.0 eq.), Ac_2O, r.t., 12 h.

C-H activation is one of the biggest topics in modern chemistry and a lot of effort has been put into this field.[198] The goal is to achieve a certain functionalization of "inert" C-H groups (R_3-CH, R_2-CH_2, R-CH_3; R = alkyl). Often, a metal is needed or a directing group. One of the earliest reported C-H activations was the Hofmann-Löffler-Freytag reaction[199] to convert a C(sp^3)-H into a C(sp^3)-N bond *via* a an alkyl halide.

For our purposes, a hydroxy function should act as the directing group. This kind of C-H activation is well documented on steroid structures *via* a hydroxy-mediated C-H activation of the methyl function in δ-position[200] **3.123** to the bridged ether **3.124** as shown in Scheme 3.18. This reaction was initially reported by Mihailovic and co-workers in 1959,[201] who formed from the secondary alcohol the bridged ether.



3.123 **3.124**

Scheme 3.18: Example of a C-H oxidation and subsequent cyclization. a) $Pb(OAc)_4$ (10% HOAc), I_2, CCl_4, reflux, 4 h.

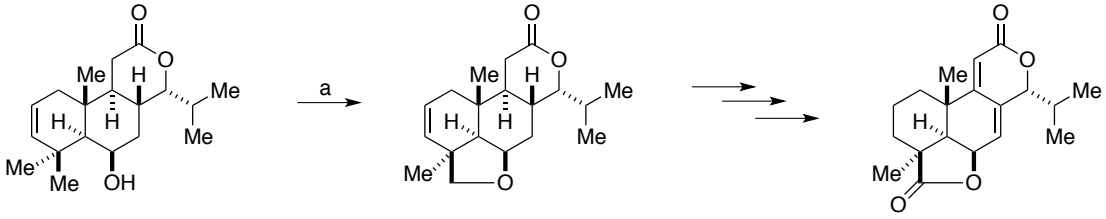
[198] a) X. Chen, K. M. Eagle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed*. **2009**, *48*, 5094; b) H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev*. **2003**, *103*, 2861.

[199] a) A. W. Hofmann, *Ber.* **1885**, *18*, 109; b) K. Löffler, C. Freytag, *Ber.* **1909**, *42*, 3427.

[200] J. Kalvoda, K. Heusler, *Synthesis* **1971**, 501.

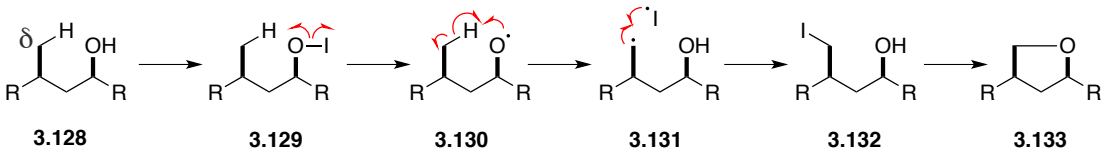
[201] a) G. Cainelli, M. Lj. Mihailovic, D. Arigoni, O. Jeger, *Helv. Chim. Acta* **1959**, *42*, 1124; b) for historical perspective on C-H activation see: Y. Ishihara, P. S. Baran, *Synlett* **2010**, 1733.

In the meantime, the toxic $Pb(OAc)_4$ could be replaced by hypervalent iodine species.[202] A hydroxy directed geminal methyl functionalization is found in the total synthesis of nagilactone F (**3.125**) as shown in Scheme 3.19.[203] The selectivity for the geminal methyl compound **3.126** to the ether bridge **3.127** was quite moderate (1:1.4) but in a good yield of 71%.



Scheme 3.19: Relay C-H activation of geminal methyl groups. a) $PhI(OAc)_2$, I_2, cyclohexane, hν, 50 °C.

The reaction follows an *in situ* generation from a hydroxy-δ-methyl **3.128** building block *via* a hypoiodite intermediate **3.129** which is cleaved to form an oxygen centered radical **3.130.** The oxygen radical will abstract a hydrogen in δ-position to yield the carbon centered radical **3.131**, which is then quenched by the iodo radical to form the iodoalkane **3.132**. A nucleophilic attack on the alkyliodide bond furnishes the cyclized product **3.133** as summarized in Scheme 3.20.[200]



Scheme 3.20: General mechanism for the iodine mediated hydroxy directed C-H activation.

[202] a) H. Togo, M. Katohgi, *Synlett* **2001**, 565; b) L. A. Paquette, L.-Q. Sun, D. Friedrich, P. B. Savage, *Tetrahedron Lett.* **1997**, *38*, 195; c) J. I. Concepón, C. G. Francisco, R. Hernández, J. A. Salazar, E. Suárez, *Tetrahedron Lett*. **1984**, *25*, 1953; d) R. L. Dorta, C. G. Francisco, R. Freire, E. Suárez, *Tetrahedron Lett*. **1988**, *29*, 5429; e) R. Hernández, J. J. Marrero, E. Suárez, *Tetrahedron Lett*. **1988**, *29*, 5979.

[203] M. E. Kort, S. M. S. Strickland, H. M. Organ, L. A. Silks, S. D. Burke, *Tetrahedron Lett*. **1994**, *35*, 1503.

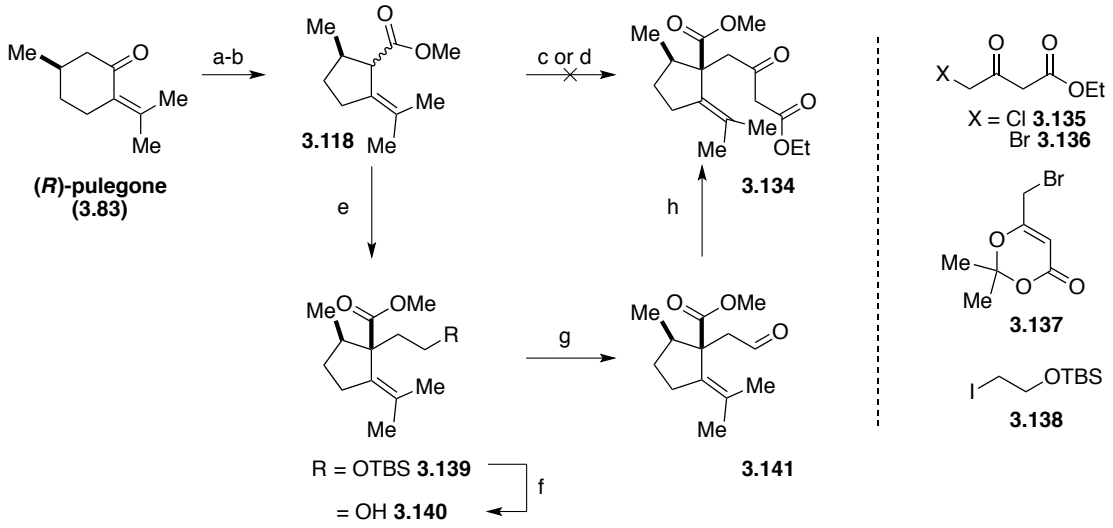
3.3.2 Synthesis of the AB-Ring System

(*R*)-Pulegone (**3.83**) was transformed *via* a Favorskii ring contraction reaction to the reported diastereomeric ester **3.118** (Scheme 3.21).[204] To our surprise, direct α-alkylation reactions on this ester was not well established and several screening condition were conducted as well different alkylating reagents were tested to form the β-ketoester **3.134**. First attempts by treating the ester with LDA and chloro ester **3.135** showed no conversion at all and the bromo ester **3.136** was tested in addition due to the higher expected reactivity, but only starting material **3.118** could be recovered. We suspect that the acidic α-protons might quench the nucleophilic enol ester. We switched to the brominated dioxin substrate **3.137** but already struggled with the preparation and only small quantities of the product could be obtained but also recovery of the starting material was observed due to the steric hindrance of the dioxin moiety. We simplified the alkylation reagent to TBS-protected iodoethanol **3.138**[205] and the alkylated ester **3.139** was indeed formed using LDA. Commercially available LiHMDS (1 M solution in THF) showed only moderate yields. Optimization of the conditions showed that addition of HMPA or DMPU to LDA was crucial for full conversion, where in the absence of an additive only one of the diastereomers was alkylated. Both additives showed comparable yields and we proceeded the reaction with DMPU due to its safer handling. TBS-protecting group was removed using TBAF to the corresponding alcohol **3.140** and then oxidized with DMP to the corresponding aldehyde **3.141** in 89% yield. Finally, a Roskamp reaction[206] furnished the desired β-ketoester **3.134** in an excellent yield of 93%. Other methods like the Reformatsky reaction were not successful on this substrate.

[204] R. M. Coates, P. R. Vettel, *J. Org. Chem.* **1980**, *45*, 5430.

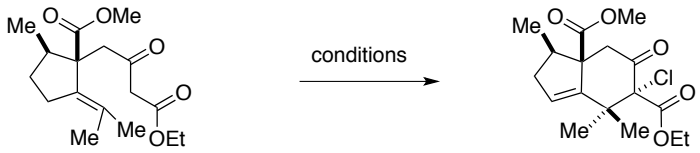
[205] C. Desroches, C. Lopes, V. Kessler, S. Parola, *Dalton Trans.* **2003**, 2085.

[206] C. R. Holmquist, E. J. Roskamp, *J. Org. Chem.* **1989**, *54*, 3258; *Tetrahedron Lett.* **1992**, *33*, 1131.



Scheme 3.21: Synthesis of the β-ketoester **3.134**. a) Br_2, $NaHCO_3$, Et_2O; b) NaOMe, MeOH, 70 °C, 3 h, 80% (over two steps); c) LDA, THF, **3.135**, –78 °C to r.t., 16 h; d) LDA, THF, **3.136**, –78 °C, to r.t., 16 h; e) LDA, DMPU, **3.138**, THF, –78 °C to r.t., 77%; f) TBAF, AcOH, CH_2Cl_2, r.t., 16 h, 79%; g) DMP, CH_2Cl_2, 4 h, 89%; h) diazoacetoacetate, $SnCl_2$ (cat.), CH_2Cl_2, r.t., 1 h, 93%.

First reactions on the manganese(III)-mediated radical cyclization of the β-ketoster **3.134** to the desired cyclized product **3.142** showed a complex mixture of products or decomposition. Isolation of the reaction mixture by flash column chromatography yielded only in inseparable products, which made further analysis of the by-products unsuitable. Nevertheless, we suggest that the by-products arise from recombination of radical intermediates. We further tried to optimize the conditions (Table 3.2) by varying the temperature (entries 2-3), solvent (entry 12), $Mn(OAc)_3$ concentration (entries 4-6), salt source (entries 7-9) or order of addition (entries 10-11) in the reaction. To our disappointment, low yields or complex mixture were observed. We suggest that the substrate itself might not be suitable for this radical reaction. The best conditions were found with 50 °C in Ac_2O yielding the cyclized product **3.142** in a moderate yield of 39% (entry 1). Using this condition, the by-product formation could be suppressed, but the yield could not be further increased. We suggest that decomposition events of the starting material and radical intermediates may have taken place.



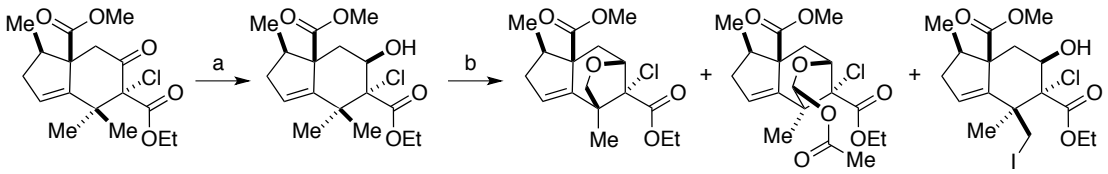
3.134 **3.142**

entry	$Mn(OAc)_3$ eq.	salt, eq.	conditions	observation
1	4.0	LiCl, 10	Ac_2O, 50 °C	39% **3.142** + polymer
2	4.0	LiCl, 10	Ac_2O, 80 °C	25% **3.142**
3	4.0	LiCl, 10	Ac_2O, 120 °C	complex mixture
4	6.0	LiCl, 10	Ac_2O, 50 °C	14% **3.142**
5	6.0	LiCl, 10	Ac_2O, 80 °C	26% **3.142**
6	8.0	LiCl, 10	Ac_2O, 50 °C	14% **3.142**
7	4.0	KCl, 10	Ac_2O, 50 °C	complex mixture
8	4.0	NaCl,10	Ac_2O, 50 °C	complex mixture
9	4.0	$CuCl_2$, 4	Ac_2O, 50 °C	complex mixture
10	4.0	LiCl, 10	Ac_2O, substrate add. over 1 h, 50 °C	24% **3.142**
11	4.0	LiCl, 10	Ac_2O, $Mn(OAc)_3$ add. over 1 h, 50 °C	decomposition
12	4.0	LiCl, 10	AcOH, 50 °C	23% **3.142** + polymer

Table 3.2: Screening conditions for the Mn(III)-mediated radical cyclization.

3.3.3 Formation of the C-Ring

Assembly of the C-ring was initiated by the reduction of the ketone **3.142** to the alcohol **3.143** (Scheme 3.22). The reduction was completely diastereoselective and the absolute configuration was confirmed by X-ray crystal structure analysis. Similar substrates behaved the same for this reduction and a coordinating effect of the chlorine can be discounted, suggested a substrate controlled reduction.[183] The alcohol **3.143** was then subjected to the regiospecific C-H activation in the presence of I_2, a low-pressure mercury lamp and $CaCO_3$. The desired hydrofuran **3.144** was obtained in 81% yield along with the by-products **3.145** and **3.146**.



Scheme 3.22: Diastereoselective reduction and C-H activation. a) $NaBH_4$, MeOH, 0 °C to r.t., 4 h, 86%; b) $Pb(OAc)_4$, I_2, $CaCO_3$, hν, r.t., 3 d, (81% **3.144**, 15% **3.145**, traces **3.146**)

The alcohol **3.143**, hydrofuran **3.144** and the acetylated furan **3.145** structures were secured by X-ray crystal structure analysis and represented in Figure 3.10.

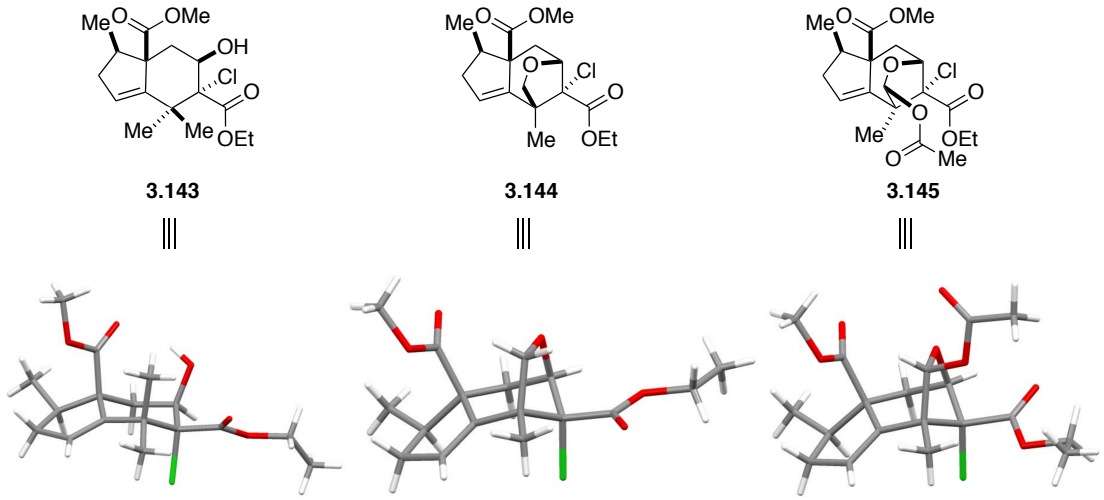
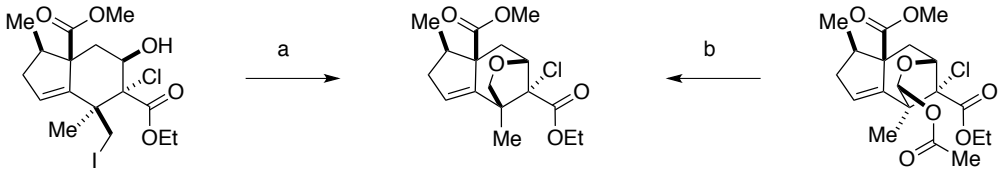


Figure 3.10: X-ray crystal structures of the alcohol **3.143**, hydrofuran **3.144** and acetylated hydrofuran **3.145** (X-ray structure color code: green = chlorine; grey = carbon; red = oxygen; white = hydrogen).

The iodo-compound **3.146** was observed when the reaction time was 5 h, which indicates that the hydrofuran **3.144** formation is formed over time. Upon a reaction time extension and a higher loading of he reagents, the iodo-compound **3.146** was only observed in traces but the acetylated by-product **3.145** was additionally formed (confirmed by X-ray crystallography structure analysis). This is formed when the methyl group undergoes a second C-H activation, which is first attacked by the hydroxy group and then by an acetyl moiety. Both by-product formations are in agreement with the review of Kalvoda and Heusler.[200] The isolated by-products could be successfully converted into the hydrofurane **3.144** in 88% yield by treating the iodo-compound **3.146** with AgOAc and the acetylated hydrofurane **3.145** with BF_3 x OEt_2[207] in 98% as shown in Scheme 3.23.



3.146 **3.144** **3.145**

Scheme 3.23: Conversion of the by-products **3.145** and **3.146** to the desired hydrofurane **3.144**. a) AgOAc, acetone, 60 °C, 10 h, 88%; b) BF_3 x OEt_2, Et_3SiH, –78 °C to r.t., 15 h, 98%.

β-Halo-ethers **3.144** can be eliminated to olefins through a Boord olefin synthesis.[208] The elimination should directly form the α,β-unsaturated lactone **3.147** as shown in Scheme 3.24. Classical elimination conditions using Zn[209] or ZnI_2[210] or alternative conditions using SmI_2,[211] $CrCl_2$,[212] Mn/TMSCl[213] or BF_3 x OEt_2 yielded only in recovery of starting material. Also by heating the reactions, the starting material remained untouched.

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[207] S. Beszant, E. Giannini, G. Zanoni, G. Vidari, *Tetrahedron: Asymmetry* **2002**, *13*, 1245.

[208] L. C. Swallen, C. E. Boord, *J. Am. Chem. Soc*. **1930**, *52*, 651.

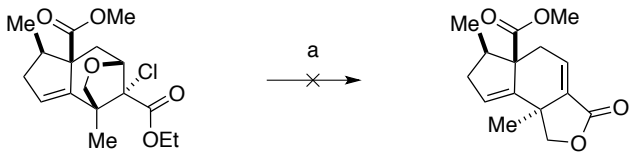
[209] M. Numazawa, K. Yamada, *Steroids* **1999**, *64*, 320.

[210] A. K. Banerjee, J. A. Azócar, M. C. Sulbarán de Carrasco, M. L. Mimó, *Synthetic Communications* **2001**, *31*, 2471.

[211] J. M. Concellón, H. Rodríguez-Solla, M. Huerta, J. A. Pérer-Andrés, *Eur. J. Org. Chem*. **2002**, 1839.

[212] J. M. Concellón, H. Rodríguez-Solla, C. Méjica, *Tetrahedron Lett.* **2004**, *45*, 2977.

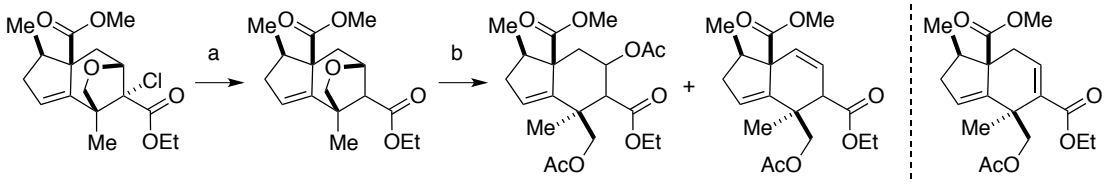
[213] J. M. Concellón, H. Rodríguez-Solla, V. del Amo, P. Díaz, *Synthesis* **2009**, *15*, 2634.



3.144 **3.147**

Scheme 3.24: Boord elimination approach. a) Zn (activated), EtOH, 90 °C, 2 h or ZnI_2, Ac_2O, r.t., 15 h or SmI_2, THF, r.t., 5 h or Mn, TMSCl, THF, 70 °C, 12 h or $CrCl_2$, THF, 70 °C, 12 h or BF_3 x OEt_2, AcOH, r.t. 5 h.

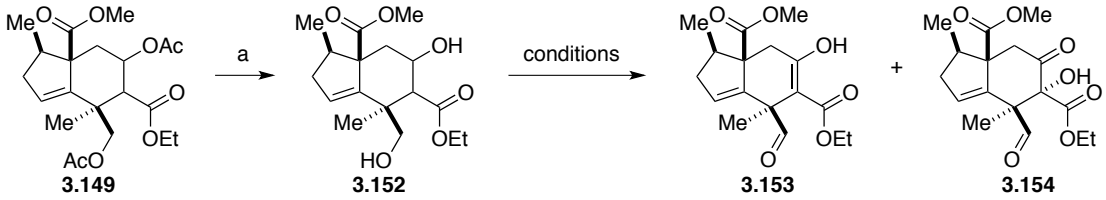
We replaced the chlorine with a hydrogen using $SnBu_3H$ to yield the α-hydrogen furan **3.148**, which gave the opportunity for further ring opening reactions (Scheme 3.25). We were pleased to see that the hydrofuran could smoothly be opened in the presence of BF_3 x OEt_2 yielding the bisacetyl **3.149** and monoacetyl-compound **3.150**. Interestingly, the same conditions were already applied on the α-chloro substrate **3.144**, but only the starting material could be recovered. The fact that with substrate **3.148**, the β,γ-unsaturated lactone **3.150** instead of the expected α,β-unsaturated lactone **3.151** is formed may be due to the more flexible structure, which is more suitable for elimination. Furthermore, basic treatment with LDA or LiHMDS to achieve elimination yielded only in recovery of the starting material, which might result from steric hindrance of the ether and ethylester moieties.



3.144 **3.148** **3.149** **3.150** **3.151**

Scheme 3.25: Hydrofuran opening. a) Bu_3SnH, AIBN, 100 °C, 2 h, 95%; b) BF_3 x OEt_2, Ac_2O, r.t., 15 h, 92% (**3.149**/**3.150** = 3:1).

Material supply and an already installed oxygen function at C-7 made further synthetic progress more suitable with substrate **3.149**. The bis-acetyl ester **3.149** was deprotected under standard conditions[214] to the diol **3.152** in 98% (Table 3.3). A bis-oxidation should readily install an aldehyde for the reductive cyclization and a β-ketoester moiety for the introduction of the alcohol in α-position. We first treated the diol **3.152** with DMP (Table 3.3, entry 1) and could isolate the desired oxidized product after flash column purification as the enol **3.153**. However, the reduction was often not reproducible and alternative conditions were tested. Adding $NaHCO_3$ (entry 2) to the reaction yielded only in a complex mixture. IBX showed a complex mixture in general, but further analysis showed the desired enol **3.153** along with another by-product, which was identified as the already α-hydroxylated product **3.154**, but only in small quantities. Swern's conditions showed only traces of the enol **3.155** but Ley-Griffith (entry 5) and Corey-Kim oxidation (entry 6) protocols showed good and reproducible yields of the enol **3.153**.

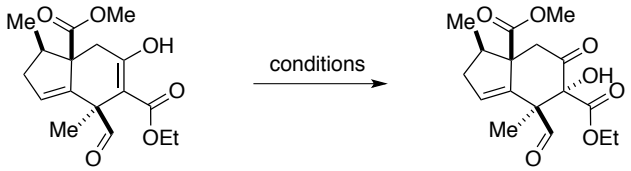


entry	reagent	conditions	observation
1	DMP	CH_2Cl_2, r.t., 3 h	56% **3.153**, not reproducible
2	DMP, $NaHCO_3$	CH_2Cl_2, r.t., 10 h	complex mixture
3	IBX	$CHCl_3$, r.t., 3 h	**3.153** and **3.154**
4	DMSO, $(COCl)_2$, NEt_3	CH_2Cl_2, –78 °C to r.t., 8 h	**3.153**, traces
5	TPAP, NMO	4Å molecular sieve, CH_2Cl_2, r.t., 16 h	68% **3.153**
6	NCS, Me_2S, NEt_3	CH_2Cl_2, –78 °C, 3 h	72% **3.153**

Table 3.3: Deprotection and bis-oxdiation attempts. a) K_2CO_3, MeOH, r.t., 16 h, 98%.

[214] D. Urabe, M. Inoue, *Tetrahedron* **2009**, *65*, 6271.

The oxidation already indicated that a α-hydroxylation of the enol **3.153** is possible and we continued our efforts next on an effective hydroxylation insertion screening as summarized in Table 3.4. However the enol **3.153** showed only limited reactivity for the described literature protocols (entries 1-5). We increased further the amount of IBX and prolonged the reaction time, but only traces of the α-hydroxylated ketone **3.154** were found (entry 6). We were then pleased that the method of Christoffer's, which produced desired compound **3.154** in traces for $CoCl_2$ (entry 7) and in reasonable yields for $CeCl_3$[215] with O_2 (entry 8) as the oxygen source.



3.153 **3.154**

entry	oxidation reagent	conditions	observation
1	*m*-CPBA[183]	CH_2Cl_2, r.t., 16 h	**3.153**
2	$Mn(OAc)_2 \cdot 4\ H_2O$, O_2[216]	CH_2Cl_2, r.t., 16 h	**3.153**
3	$Mn(OAc)_3 \cdot 2\ H_2O$, O_2	AcOH, r.t., 8 h	**3.153**
4	OsO_4, NMO[189]	*t*-BuOH, H_2O, r.t., 16 h	**3.153**
5	Davis oxaziridine, LDA[217]	THF, –25 °C to r.t., 16 h	**3.153**
6	IBX	DMSO, r.t., 16 h	traces of **3.154**
7	$CoCl_2$, oxygen[218]	MeCN, ^{i}PrOH, 60 °C, 16 h	traces of **3.154**
8	$CeCl_3 \cdot 7\ H_2O$, oxygen[215]	^{i}PrOH, r.t., 17 h	43% **3.154**

Table 3.4: α-Hydroxylation attempts.

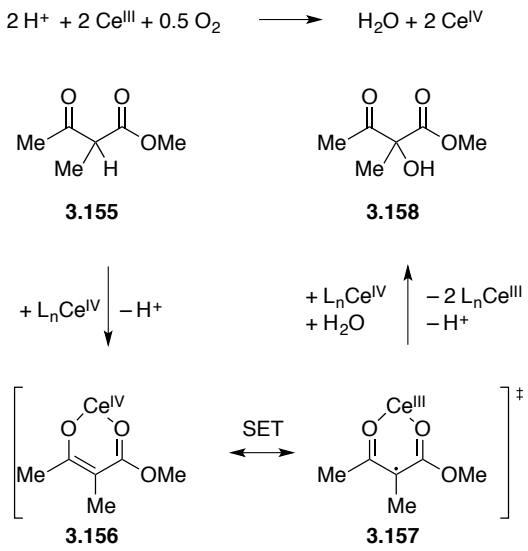
[215] J. Christoffers, T. Werner, *Synlett* **2002**, *1*, 119.

[216] J. Christoffers, *J. Org. Chem*. **1999**, *64*, 7668.

[217] F. A. Davis, M. S. Haque, T. G. Ulatowski, J. C. Towson, *J. Org. Chem*. **1986**, *51*, 2402.

[218] X. Bacherel, E. Levoirier, J. Uziel, S. Juge, *Tetrahedron Lett.* **2000**, *41*, 1385.

The proposed mechanism[219] is depicted in Scheme 3.26. The oxygen acts as the oxidant and converts Ce(III) to Ce(IV), which forms with β-ketoester **3.155** an enol-Ce(IV) intermediate **3.156** and a ligand-to-metal electron transfer (SET) occurs. The electrophilic α-radical **3.157** is then trapped by the nucleophilic water, which introduces the hydroxy function **3.158**.[220]



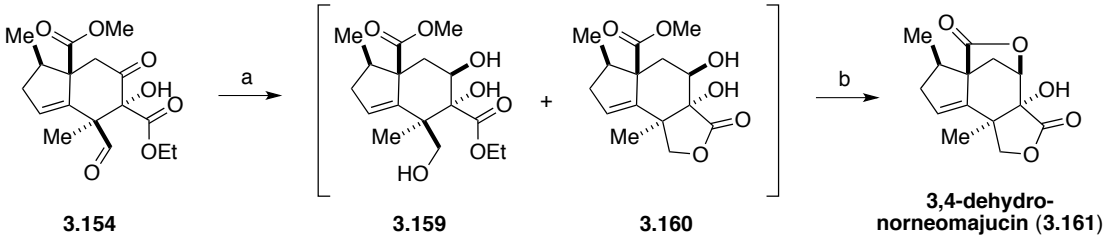
Scheme 3.26: Proposed Ce(III) radical α-hydroxylation mechanism.[219]

3.3.4 Assembly of the ABCD-Ring System

With the α-hydroxylated compound **3.154** in hand, we assumed that a reductive cyclization from the aldehyde to the ethylester should be highly favored (Scheme 3.27). However, a complex mixture of the triol **3.159** and cyclized product **3.160** was observed. This crude mixture was directly subjected to an acid catalyzed lactonization reaction to form the desired ABCD-ring **3.161** assembly in a low yield of 27% over two steps. A reason for the low yield could arise from solubility issues or instability of the triol **3.159**. Due to material supply issues, we couldn't further optimize these reaction conditions.

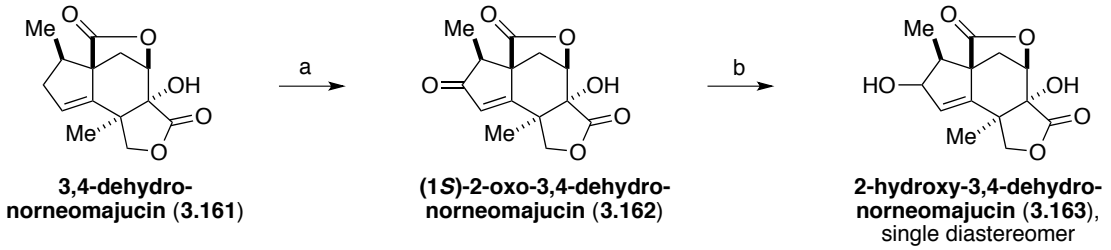
[219] J. Christoffers, T. Werner, S. Unger, W. Frey, *Eur. J. Org. Chem.* **2003**, 425.

[220] J. Christoffers, T. Kauf, T. Werner, M. Rössle, *Eur. J. Org. Chem.* **2006**, 2601.



Scheme 3.27: Reduction and lactonization to obtain the ABCD-ring system **3.161**. a) $NaBH_4$, MeOH, 0 °C to r.t., 16 h; b) *p*-TsOH, PhMe, microwave, 70 °C, 2 h, 27% (over two steps).

The olefin **3.161** was oxidized in allylic position to the enone **3.162** as shown in Scheme 3.28. A portion of the olefin **3.161** could be recovered and the yield was not determined due to the small reaction scale. The enone **3.162** was further reduced using Luche conditions, yielding the allylic alcohol **3.163** as a single diastereomer. However, NOESY-NMR and coupling constant analysis could not fully confirm the stereocenter orientation. In this sequence, we completed the synthesis of 3,4-dehydro-norneomajucin (**3.161**) and (1*S*)-2-oxo-3,4-dehydro-norneomajucin (**3.162**), which represents two *nor*-sesquiterpenes that will be evaluated for their neurotrophic properties. A third *nor*-sesquiterpenes was obtained, namely 2-hydroxy-3,4-dehydro-norneomajucin (**3.163**), with unknown configuration at C-2 position.

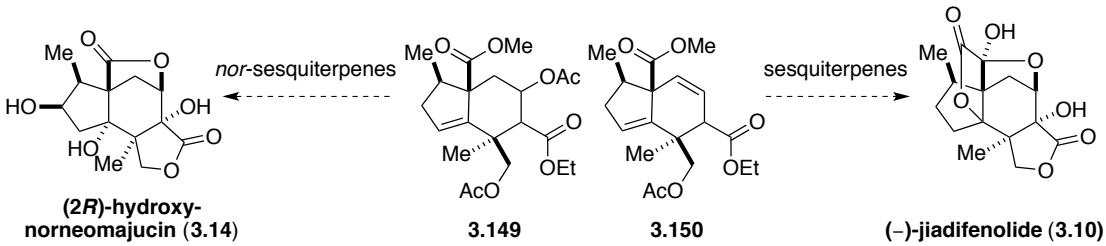


Scheme 3.28: Allylic oxidation of the bislactone **3.161** followed by Luche reduction**.** a) CrO_3, 3.5-DMP, CH_2Cl_2, r.t., 72 h, n.d.; b) $CeCl_3$ x 7 H_2O, $NaBH_4$, MeOH/THF, –78 °C, 3 h, yield n.d.

3.3.5 C1-Homologation Attempts Towards (–)-Jiadifenolide

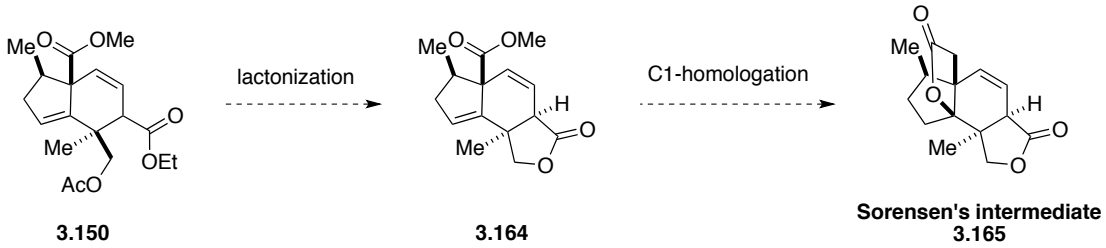
After a careful analysis of the hydrofuran **3.148** opening reaction, we saw that both products **3.149** and **3.150** can act as precursors for the synthesis of *seco*-prezizaanes as shown in Scheme 3.29. The diacetyl-compound **3.149** can be further used to access the target structure (2*R*)-hydroxynorneomajucin (**3.14**), as most of the required oxygens are already placed. The eliminated

product **3.150** would be an ideal precursor for the sesquiterpene series such as (−)-jiadifenolide (**3.10**), because the C1-homologation of the methyl ester moiety would be much less problematic.



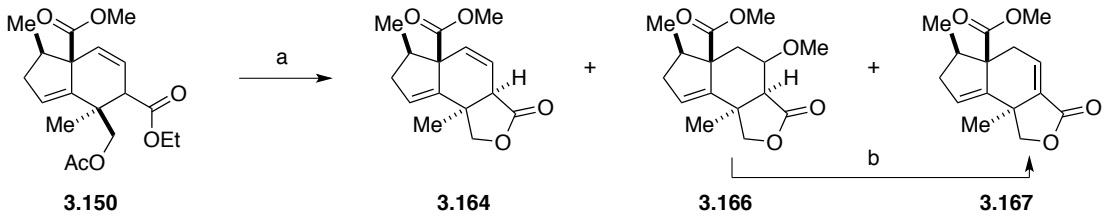
Scheme 3.29: Strategic intermediates for the synthesis of *nor*-sesquiterpenes and sesquiterpenes.

We first envisioned first to close the lactone moiety to the C-ring **3.164** and then a C1-homologation on the methyl ester-moiety to target intermediate **3.165** in Sorensen total synthesis of (−)-jiadifenolide (**3.10**),[190] as shown in Scheme 3.30.



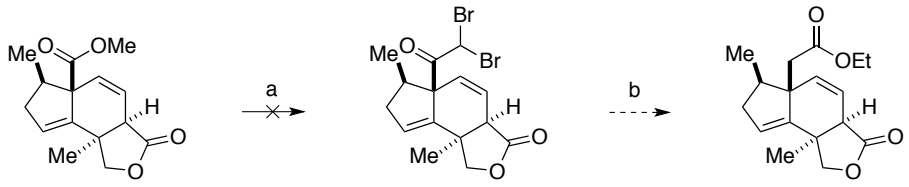
Scheme 3.30: C-ring formation and C1-homologation approach to target an advanced Sorensen's intermediate **3.165** towards a formal synthesis of (−)-jiadifenolide (**3.10**).

The acetyl deprotection of **3.150** using standard condition (K_2CO_3, MeOH) yielded in three C-ring products with **3.164** (confirmed by X-ray crystal structure analysis) as the major product (Scheme 3.31). Due to small quantities of compounds **3.166** and **3.167** we did not further investigate these products and continued our studies with substrate **3.164**.



Scheme 3.31: C-ring formation**.** a) K_2CO_3, MeOH, r.t., 16 h, 37% of **3.164**, (**3.166** and **3.167** yield n.d; b) DBU, toluene, microwave, 110 °C, 12 h, yield n.d.

The methyl ester **3.164** can be manipulated in several ways for a C1-homologation. Kowalski and co-workers reported on a direct C1-homologation of the reaction. However, this method is only rarely described in literature.[221] The sequence attempted is shown in Scheme 3.32. However, monitoring the reaction by NMR or ESI-MS showed never the α-bromo ketone **3.168** or the desired product **3.169**. The dense shape of the molecule makes probably a nucleophilic attack of the reagents not feasible.

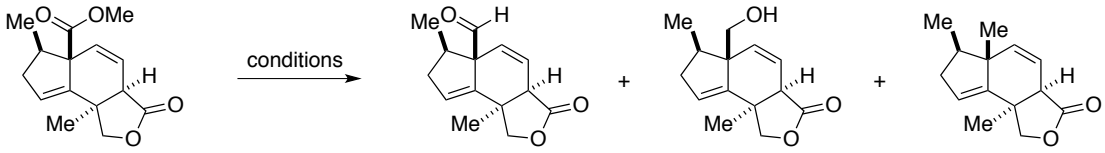


3.164 **3.168** **3.169**

Scheme 3.32: Kowalski's ester homologation method. a) CH_2Br_2, LiTMP, THF, –78 °C; b) LiHMDS, *n*-BuLi, EtOH.

We therefore switched to more common method for the C1-homologation such as reduction of the ester to an alcohol or aldehyde. The conditions and reaction is summarized in Table 3.5. Standard conditions using DIBAL-H (entries 1-6) yielded only in recovery of the starting material **3.164** or the complete reduced methyl functionality **3.170**. Other reducing reagents (entries 7-11) were not feasible to selectively obtain the desired aldehyde **3.171** or alcohol **3.172**, and only the starting material **3.164** was recovered or a complex mixture was observed. Only super-hydride® (entry 12) showed traces of the aldehyde **3.171**, unfortunately these result could not be reproduced. We concluded that the methyl ester is too sterically hindered already for a simple hydride and did not further investigate reductions or methyl ester manipulation.

[221] C. J. Kowalski, M. Serajul Haque, K. W. Fields, *J. Am. Chem. Soc.* **1985**, *107*, 1429.

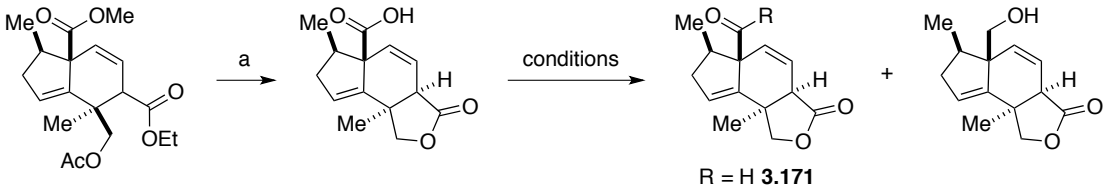


3.164 **3.171** **3.172** **3.170**

entry	reductant	conditions	observation
1	DIBAL-H	CH_2Cl_2, –78 °C to r.t., 16 h	**3.170**
2	DIBAL-H	CH_2Cl_2, –78 °C to r.t., 8 h	**3.170**
3	DIBAL-H	CH_2Cl_2, –78 °C to –40 °C, 4 h	**3.170**
4	DIBAL-H	CH_2Cl_2, –78 °C, 3 h	**3.164** and **3.170**
5	DIBAL-H	THF, –78 °C, 2 h	**3.164**
6	DIBAL-H	THF, –78 °C to 0°C, 12 h	**3.170**
7	L-selectride	CH_2Cl_2, –78 °C to –40 °C, 4 h	**3.164**
8	Red-Al	CH_2Cl_2, –78 °C to –40 °C, 4 h	**3.164**
9	$LiAlH_4$	THF, –78 °C to 0 °C, 2 h	decomposition
10	LAB	THF, –20 °C, 3 h	**3.164**
11	LAB	THF, r.t., 3 h	complex mixture
12	Super-hydride®	CH_2Cl_2, –78 °C to –40 °C, 4 h	traces of **3.171** and by-products

Table 3.5: Ester reduction conditions.

We targeted next the free carboxylic acid **3.173** as a suitable C1-homologation precursor. The methylester **3.150** was saponificated with NaOH/^{i}PrOH to yield the desired carboxylic acid **3.173** and we could observe that the C-ring was directly formed in an excellent yield of 88%. Further attempts to reduce the carboxylic acid **3.173** to the aldehyde **3.171** or alcohol **3.172** were not successful (Table 3.6). DMS as a reducing reagent (entry 1) yielded only a complex mixture, as well as for super-hydride® (entry 2). Other conditions *via* the synthesis of the mixed anhydride and subsequent reduction to the alcohol is a known way to form alcohols from carboxylic acids. In our case, the mixed anhydride **3.174** was obtained (entry 3), but seemed to be quite unreactive under further reducing conditions. We next used a less sterically hindered anhydride but could never obtain the desired alcohol **3.172** or mixed anhydride **3.175** and only the starting material **3.173** could be recovered (entries 4 and 5).



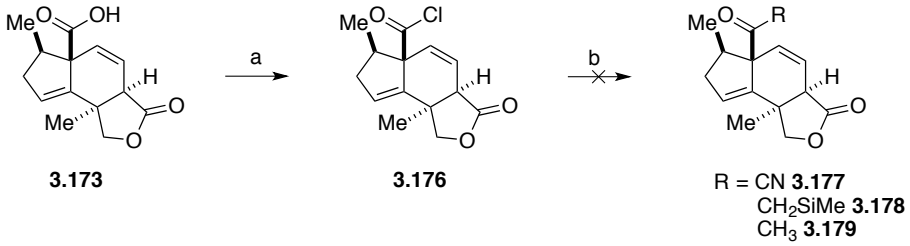
3.150 **3.173** **3.172**

entry	reducing agent	conditions	observation
1	DMS	THF, 0 °C to r.t.	complex mixture
2	Super-hydride®	CH_2Cl_2, –78 °C, 3 h	complex mixture
3	NMM, ClC(O)O*i*-Bu, Et_3N, $NaBH_4$	THF, 0 °C to r.t.	**3.174**
4[222]	NMM, ClC(O)OMe, Et_3N, $NaBH_4$	THF, 0 °C to r.t.	**3.173**
5	NMM, ClC(O)OMe, Et_3N, $LiBH_4$	THF, 0 °C to r.t.	**3.173**

Table 3.6: C-ring formation and carboxylic acid **3.175** reduction attempts. a) NaOH, ^{i}PrOH, r.t., 16 h, 81%.

[222] K. Prantz, J. Mulzer, *Angew. Chem. Int. Ed. Engl.* **2009**, *48*, 5030.

The unreactivity towards several reducing conditions led finally to synthesis of the acyl chloride **3.176** by treating the carboxylic acid **3.173** with thionylchloride (Scheme 3.33). The crude acyl chloride **3.176** was then treated with Me_3SiCN[223], Me_3SiCH_2Li[224] or MeLi but only the quenched carboxylic acid **3.173** was observed instead of the desired homologated products **3.177**, **3.178** or **3.179**.



3.173 **3.176**

R = CN **3.177**
CH_2SiMe **3.178**
CH_3 **3.179**

Scheme 3.33: C1-homologation attempts on the acid chloride **3.176** moiety**.** a) $SOCl_2$, CH_2Cl_2, 60 °C, 6 h; b) Me_3SiCN (R = CN) or Me_3SiCH_2Li (R = CH_2SiMe_3) or MeLi (R = Me).

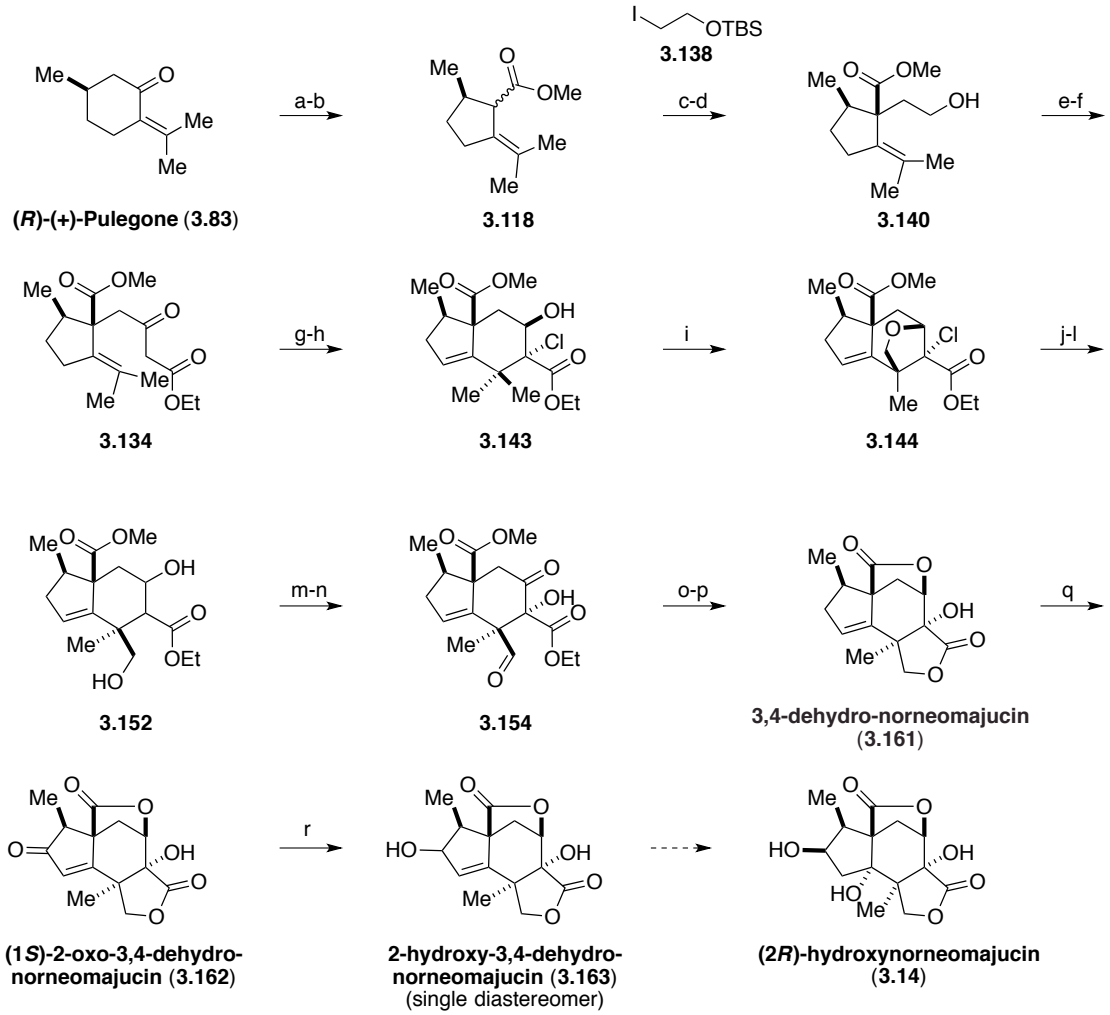
To conclude, the C1-homologation was tested on several substrates (**3.164**, **3.173** and **3.176**) but mostly the substrates were inert to any applied conditions (reduction, mixed anhydride, etc.). We propose that the ABC-ring system is shielding the carbonyl moiety towards nucleophiles. We therefore did not further investigate methyl ester **3.164** as a potential precursor for the synthesis of *seco*-prezizaane type sesquiterpenes.

[223] K. Herrmann, G. Simchen, *Synthesis* **1979**, *3*, 204.

[224] M. Obayashi, K. Utimoto, H. Nozaki, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2646.

3.4 Conclusion and Outlook

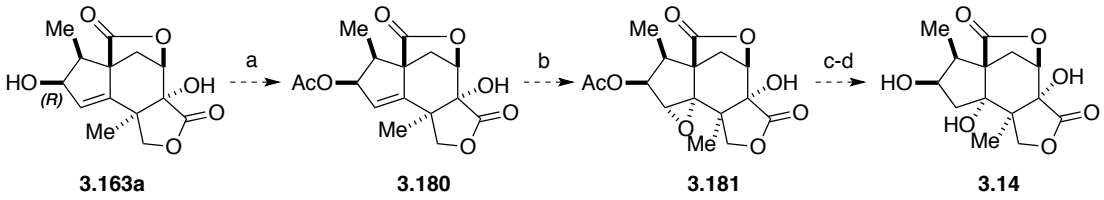
In this project, the progress towards natural product-derived neurotrophins has been demonstrated. Several members of the genus *Illicium* are highly active neutrophic molecules and therefore, should be considered as potential treatment for neurodegenerative diseases, such as Alzheimer's and Parkinson's disease. (2*R*)-Hydroxynorneomajucin (**3.14**) represents a rare *nor*-sesquiterpenoid, which is a highly active neurotrophic modulator. The structure is of special interest, because *nor*-sesquiterpenoids are much less reported than their well-established sesquiterpene analogues. The presented synthesis herein was designed to target specifically *nor*-type structures and to create an activity map of *nor*-sesquiterpenoids. Our synthesis towards (2*R*)-hydroxynorneomajucin (**3.14**) is shown in Scheme 3.34. For the first 16 steps, an overall yield of 0.5% was obtained. Starting from enantiopure (*R*)-pulegone (**3.83**), the C2-unit **3.138** was introduced to the racemic ester **3.118** and after deprotection of the TBS-protecting group, the free alcohol **3.140** was obtained. Synthesis of β-ketoester **3.134** involved a Roskamp reaction. A manganese(III)-mediated 6-*endo*-*trig* radical cyclization furnished the B-ring structure and alcohol **3.143** was obtained after a diastereoselective ketone reduction. A regiospecific, hydroxy-directed sp^3 C-H activation gave the hydrofuran **3.144**. Replacement of the chlorine by a hydrogen, opening of the hydrofurane ring and deprotection of the acetyl moieties furnished diol **3.152**. The α-hydroxy group was inserted *via* a Ce-mediated hydroxylation to the α-hydroxyketone **3.154**. A reductive cyclization furnished the ABCD-ring core **3.161** of *nor*-sesquiterpenoid structures. This intermediate can be used as intermediate for further SAR-studies on *nor*-sesquiterpenoids. Furthermore three *nor*-sesquiterpenes, namely 3,4-dehydro-norneomajucin (**3.161**), (1*S*)-2-oxo-3,4-dehydro-norneomajucin (**3.162**) and 2-hydroxy-3,4-dehydro-nor-neomajucin (**3.163**) were synthesized and will be tested on their neurotrophic behavior.



Scheme 3.34: Synthetic progress towards (2*R*)-hydroxynorneomajucin (**3.14**). a) Br_2, $NaHCO_3$, Et_2O, 0 °C, 1 h; b) NaOMe, MeOH, reflux; 3 h; 72% (over two steps); c) LDA, DMPU, **3.138**, THF, –78 °C to r.t., 77% (single diastereomer); d) TBAF, THF, 0 °C to r.t., 18 h, 79%; e) DMP, CH_2Cl_2, r.t., 2 h, 89%; f) ethyl diazoacetate, $SnCl_2$ (cat), CH_2Cl_2, r.t., 12 h, 93%; g) $Mn(OAc)_3$, LiCl, Ac_2O, 50 °C, 39%; h) $NaBH_4$, MeOH, 0 °C to r.t., 4 h, 86%; i) $Pb(OAc)_4$, I_2, $CaCO_3$, hν, 72 h, 95%; j) AIBN, Bu_3SnH, PhH, 100 °C, 2 h, 95%; k) BF_3 x OEt_2, Ac_2O, r.t., 15 h, 60%; l) K_2CO_3, MeOH, r.t., 16 h, 98%; m) NCS, Me_2S, NEt_3, –78 °C to r.t., 72%; n) $CeCl_3 \cdot 7\ H_2O$, O_2, ^{i}PrOH, r.t., 24 h, 43%; o) $NaBH_4$, MeOH, 0 °C to r.t., 12 h; p) *p*-TsOH, toluene, 70 °C, microwave, 2 h, 27% (over two steps); q) CrO_3, 3.5-DMP, CH_2Cl_2, r.t., 72 h, n.d.; r) $CeCl_3$, $NaBH_4$, MeOH/THF, –78 °C, 3 h, yield n.d.

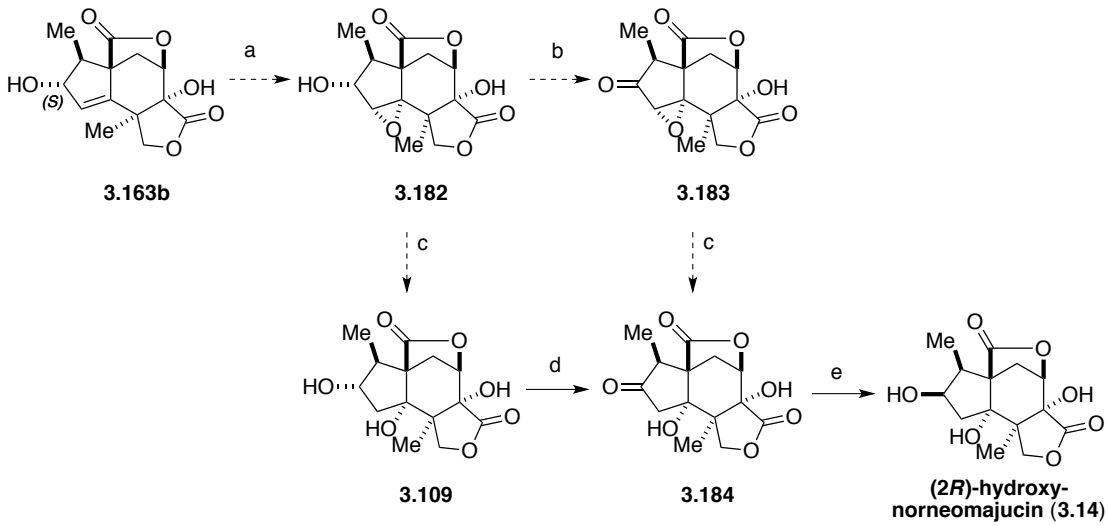
Due to time and material supply issues, the further steps towards (2*R*)-hydroxynorneomajucin (**3.14**) could not be continued. Left to be completed is determination of the stereocenter in allylic alcohol **3.163**. In case of a (*R*)-configured alcohol **3.163a**, the alcohol is protected **3.180** and the olefin

epoxidized **3.181**, followed by epoxide opening and deacetylation should furnish the target molecule (2*R*)-hydroxynorneomajucin (**3.14**, Scheme 3.35).



Scheme 3.35: Proposed synthesis towards (2*R*)-hydroxynorneomajucin (**3.14**) from (*R*)-configured alcohol **3.163a**. a) acetylation; b) epoxidation; c) epoxide opening; d) deacetylation.

For a (*S*)-configured alcohol **3.163b**, a hydroxy directed epoxidation to form epoxide **3.182** would be applied, followed by an epoxide opening to the known triol **3.109** (Scheme 3.36). Otherwise, the hydroxyepoxide **3.182** can be further oxidized to the ketone **3.183** and the epoxide opened to the β-hydroxyketone **3.184**. Substrates **3.109** and **3.184** are already known in literature as well as their further conversion to the final molecule (2*R*)-hydroxynorneomajucin (**3.14**).[181]



Scheme 3.36: Proposed synthesis towards (2*R*)-hydroxynorneomajucin (**3.14**) from (*S)*-configured alcohol **3.163b**. a) epoxidation; b) oxidation; c) epoxide opening; d) oxidation; e) reduction.

4 Preparation of Antimalarial Endoperoxides by a Formal [2 + 2 + 2] Cycloaddition

4.1 Introduction

4.1.1 Malaria

Malaria is a parasitic infectious disease[225] and is still a public health problem of which almost half of earth's population (3.2 billion people) is at risk of. Symptoms (fever, sweat, headache, vomiting, diarrhea, muscle pain and death) are developed after an incubation time of one to three weeks. Since malaria is still not curable, the WHO global anti-malaria program[226] focused on suppression of its spreading and achieved promising results. The number of malaria cases dropped from 262 to 214 millionen cases (2000 – 2015), a decline of 18%. Even more satisfying is the decrease of reported deaths from 839'000 to 438'000 (2000 – 2015), a decline of 48%. Around 80% of these deaths arose from 15 countries, mainly in Africa.

The name malaria is derived from the Italian mal' aria (bad air, introduced by Giovanni Maria Lancisi in 1717),[227] which has its origin from foul-smelling swamps near Rome and it is speculated that malaria (known as "Roman fever") had a tremendous impact of the fall of the Roman empire.[228] The elucidation of the malaria infection pathway was identified by Sir Ronald Ross (1857 – 1932).[229] He was awarded for his pioneering work with the Nobel Prize in Physiology or Medicine in 1902 "*for his work on malaria, by which he has shown how it enters the organism and thereby has laid the foundation for*

[225] For a historical review of malaria see: E. Hempelmann, K. Krafts, *Malaria Journal* **2013**, *12*, 232.

[226] World Malaria report WHO **2015**.

[227] E. Ferroni, T. Jefferson, G. Gachelin, *J. R. Soc. Med*. **2012**, *105*, 35.

[228] R. Carter, K. N. Mendis, *Clin. Microbiol. Rev*. **2002**, *15*, 564.

[229] E. Capanna, *International Microbiology* **2006**, *9*, 69.

successful research on this disease and methods of combating it".[230] However, Ross only described the infection of birds and not of humans. The complete life cycle of the parasite *Plasmodium falciparum* and its vector, the mosquito *Anopheles claviger*, was discovered by the italian physician and zoologist Giovanni Battista Grassi (1854 – 1925).[231] The subtype *Anopheles gambiae* is the most effective vector and therefore the most dangerous one, because it needs human blood to feed their offspring. Malaria is caused by a protozoan (single-celled) parasite from the *Plasmodium* family. The most common are *Plasmodium falciparum*, which is also the deadliest, and *Plasmodium vivax*. Malaria can be detected[232] by blood staining (Figure 4.1)

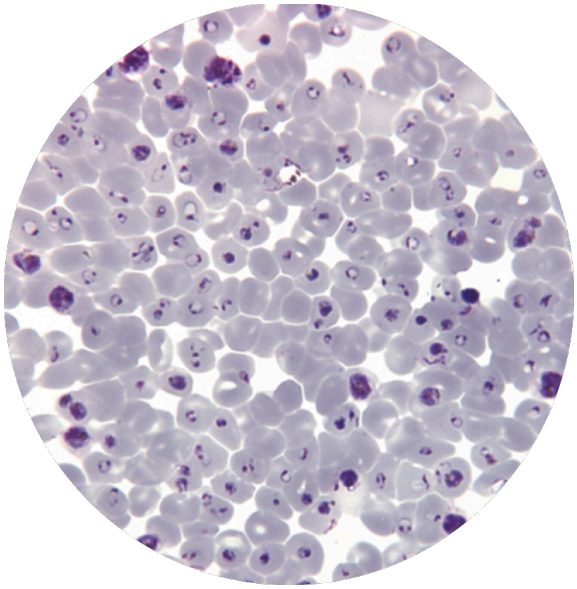


Figure 4.1: Infected cells by *P. falciparum.* Purple spots = biomineralization "malaria-pigment".[233]

The parasite itself cannot be seen by this method, but is indirectly detected by the dark violet spots, the so called "malaria-pigment". In the mature step of

[230] "Ronald Ross - Facts". Nobelprize.org. Nobel Media AB 2014. Web. 26 Apr 2016. <http://www.nobelprize.org/nobel_prizes/medicine/laureates/1902/ross-facts.html>

[231] F. E. G. Cox, *Parasites & Vectors* **2010**, *3*, 5.

[232] a) N. Tangpukdee, C. Duangdee, P. Wilairatana, S. Krudsood, Korean, *J. Parasitol.* **2009**, *47*, 93; b) C. Wongsrichanalai, M. J. Barcus, S. Muth, A. Sutamihardja, W. H. Wernsdorfer, *Am. J. Trop. Med. Hyg*. **2007**, *77*, 119.

[233] Picture provided by Dr. Marcel Kaiser, Swiss Tropical and Health Institute Switzerland.

the parasite, hemoglobin is degraded by proteases to amino acids and peptides needed for the further parasite development. A formed product in this process is heme(Fe(II)) and upon dimerization forms hematin(Fe(III)), which is toxic to the parasite. The parasite evolved a mechanism to circumvent the toxicity by a biomineralization process to form non-toxic hemozoin (malaria-pigment), which can be stained to indirectly identify the malaria infection.[234]

4.1.2 Life Cycle of the Parasite

The parasite life cycles[235] involves various stages and forms as depicted in Figure 4.2.

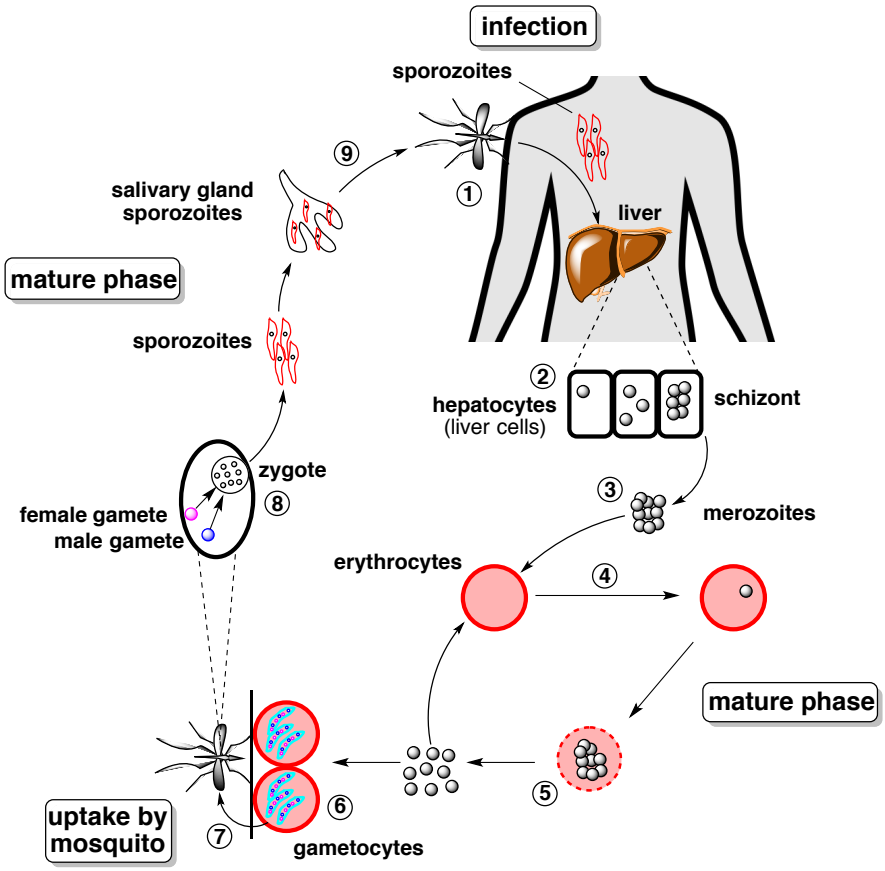


Figure 4.2: Schematic life cycle of the malaria parasite.

Malaria parasites are first transmitted *via* the bite (saliva) of an infected female *Anopheles* mosquito (1). The released sporozoites infect the hepatocytes (liver cells) and mature into forms called schizont (2). Each

[234] P. M. O'Neill, V. E. Barton, S. A. Ward, *Molecules* **2010**, *15*, 1705.

[235] T. F. de Koning-Ward, P. R. Gilson, B. S. Crabb, *Nat. Rev. Microbiol.* **2015**, *13*, 373.

schizont multiplies into thousands of their next form named merozoites (3). At this stage, the merozoites destroy hepatocyte cell and get released in the bloodstream, where they infect the erythrocytes (blood cells) (4). The parasites grow further, multiply and finally rapture the blood cell (5). So far only asexual replication occurred, where at this stage the parasite can replicate into male or female gametocytes (sexual pathway) (6). The anopheles mosquito then again takes up these sexual divided parasites from the bloodstream (7), where finally a combination of the gametocytes into a zygote occurs (8) and further processes finally releases again sporozoites into the saliva of the *Anopheles* mosquito (9). All these life cycle stages are potential treatments opportunities to combat the parasite in human and mosquito. However, due to the complex life cycle, each stage (liver cells, erythrocytes, blood stream etc.) had to be targeted specifically by the antimalarial drug. Otherwise not treated parasite forms will be still able to infect further tissues and the life cycle of the parasite starts again. An ideal drug should therefore combat at all mature stages with full effectivity.[236]

4.1.3 Malaria Prevention Strategies

The inhibition of malaria and its parasite can be addressed indirectly by treating their vector, the *Anopheles* mosquito. The so-called vector management control involves different strategies.[237] An early method was the use of dichlorodiphenyltrichloroethane [238] (DDT, **4.1**, Scheme 4.1), synthesized from chlorobenzene (**4.2**) and chloral (**4.3**). DDT **4.1** acts as a contact poison and was sprayed on house walls, where it gets in contact with the *Anopheles* mosquito. However, DDT **4.1** seems to be involved in cancer development and birds die, and therefore not often used anymore for malaria treatment.[239]

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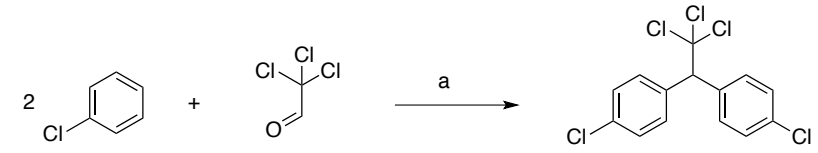
[236] M. A. Biamonte, J. Wanner, K. G Le Roch, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2829.

[237] F. Castelli, S. Odolini, B. Autino, E. Foca, R. Russo, *Pharmaceuticals* **2010**, *3*, 3212.

[238] O. Zeidler, *Berichte der deutschen chemischen Gesellschaft* **1874**, *7*, 1180.

[239] a) H. Bouwman, R. Bornan, H. van den Berg, H. Kylin, *Environmental Health Perspectives* **2011**, *119*, 744; b) C. S. Berry-Cabán, *Journal of Military and Veteran's Health* **2011**, *19*, 19.



chlorobenzene (4.2) **chloral (4.3)** **DDT (4.1)**

Scheme 4.1: Synthesis of DDT (**4.1**) by Othmar Zeidler in 1874. a) H_2SO_4 (cat.).

Another approach is the use of a net during sleep. This method prevents to get bitten by the mosquito during night, which is the active time of the mosquito. A biological approach for the combat of malaria is the use of larvivorous fishes, which are eating the larvae and pupae of the anopheles mosquito in water. However, the release of fishes into a new environment can tremendously influence the biological balance of the habitat.[226]

4.1.4 Small Molecules as Potential Malaria Treatment Candidates

Early malaria prevention was already reported in the 17th century. The extracts of the quina-quina bark had a positive effect on the malaria symptoms and quinine (**4.4**) was isolated as the active antimalarial agent (Figure 4.3).[240] Methylene-blue (**4.5**) was the first fully synthetic compound[241] used against malaria. Paul Guttmann and Paul Ehrlich used in 1891 methylene-blue (**4.5**) as the first malaria parasite stain and concluded that methylene-blue (**4.5**) also might be harmful to the parasite. However, it was not as effective as quinine (**4.4**).[242]

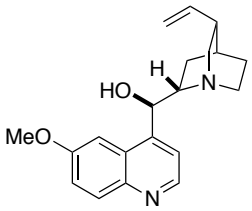
A major contribution and a beginning of a new antimalarial treating era was the discovery of chloroquine (**4.6**) (or Resochin, from it's salt resorcinate of a 4-aminochinolin). Johann "Hans" Andersag (1902 – 1955) synthesized chloroquine (**4.6**) at the pharmaceutical company Bayer in 1934 and it is still one of the most used antimalarial agents up to today. Chloroquine (**4.6**)

[240] J. Achan, A. O. Talisuna, A. Erhart, A. Yeka, J. K. Tibenderana, F. N. Baliraine, P. J. Rosenthal, U. D'Alessandro, *Malaria Journal* **2011**, *10*, 144.

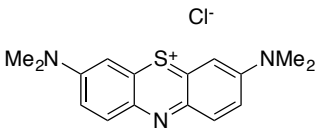
[241] R. H. Schirmer, H. Adler, M. Pickhardt, E. Mandelkow, *Neurobiol. Aging* **2011**, *32*, *2325.e7–2325.e16.*

[242] K. Krafts, E. Hempelmann, A. Skórska-Stania, *Parasitol. Res*. **2012**, *111*, 1.

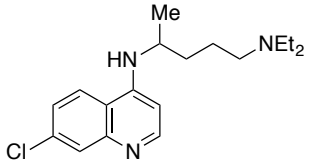
interrupts the biocrystallization of the non-toxic hemozoin (malaria-pigment) by binding to heme, which then still can act as antimalarial agent.[243] Nevertheless, chloroquine (**4.6**) resistant parasite strains are reported and chloroquine (**4.6**) is nowadays used in combination with other antimalarial compounds such as artemisinin (**1.9**).[226]



quinine (4.4)



methylene-blue (4.5)



chloroquine (4.6)

Figure 4.3: First malaria preventing agents.

Artemisinin (**1.9**) (Scheme 4.2) was isolated from *Artemisia annua* (qinghaosu) [244] and is a sesquiterpene lactone with a characteristic endoperoxidal motif.[245] The structure consists of five oxygen atoms, which are parts of cyclic ether, peroxy ether, a lactone as well as a cyclic acetal and ketal moiety. Initial structure studies showed that the peroxy bridge is crucial for the antimalarial activity and its reduced ether analogue completely lost its antimalarial activity.[246]

The discovery and further beneficial applications for human health was then awarded with the Nobel Prize in Physiology or Medicine 2015 for Youyou Tu "*for her discoveries concerning a novel therapy against Malaria*". [247] Artemisinin (**1.9**) is one of the most common drugs for malaria treatment.

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[243] D. J. Sullivan Jr., I. Y. Gluzman, D. G. Russell, D. E. Goldberg, *Proc. Natl. Acad. Sci*. **1996**, *93*, 11865.

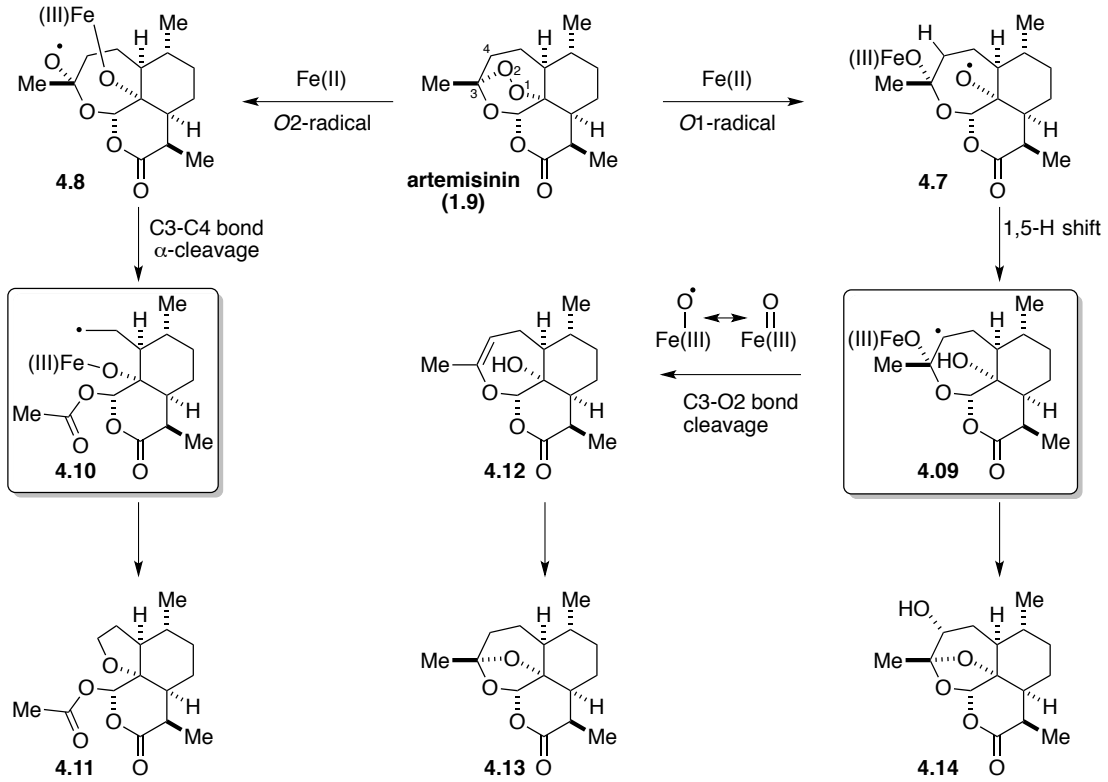
[244] C-ORGo, *Chin. Med. J. (Engl.)* **1979**, *92*, 811.

[245] a) J. M. Liu, M.-Y. Ni, Y.-Y. Tou, Z.-H. Wa, Y.-L Wu, W. S. Chou, *Acta Chim. Sinica* **1979**, *37*, 129; b) D. L. Klayman; A. J. Lin, N. Acton, J. P. Scovill, J. M. Hoch, W. K. Milhous, A. D. Theoharides, A. S. Dobek, *J. Nat. Prod*. **1984**, *47*, 715; c) Y. Tu, *Nat. Med.* **2011**, *17*, 1217.

[246] Z. Guo, *Acta Pharmaceutica Sinica B* **2016**, *6*, 115.

[247] "Youyou Tu - Facts". Nobelprize.org. Nobel Media AB 2014. Web. 26 Apr **2016**. <http://www.nobelprize.org/nobel_prizes/medicine/laureates/2015/tu-facts.html>

The possible artemisinin (**1.9**) interaction and degradation is shown in Scheme 4.2. It is proposed that the endoperoxide bridge is cleaved to elaborate a *O*1- or *O*2-centered-radical species (**4.7** and **4.8**). Upon rearrangement, *C*-centered radicals are formed (**4.9** and **4.10**) and these species are postulated to recombine with multiple molecules (degradation products **4.11**, **4.12**, **4.13** and **4.14**) within the cell and initiates the parasites death.[248] The selectivity of artemisinin (**1.9**) towards infected erythrocytes arises from the presence of heme(Fe(II)), due to parasitic hemoglobin degradation, whereat healthy tissues contain the intact oxyhemoglobin.[249]

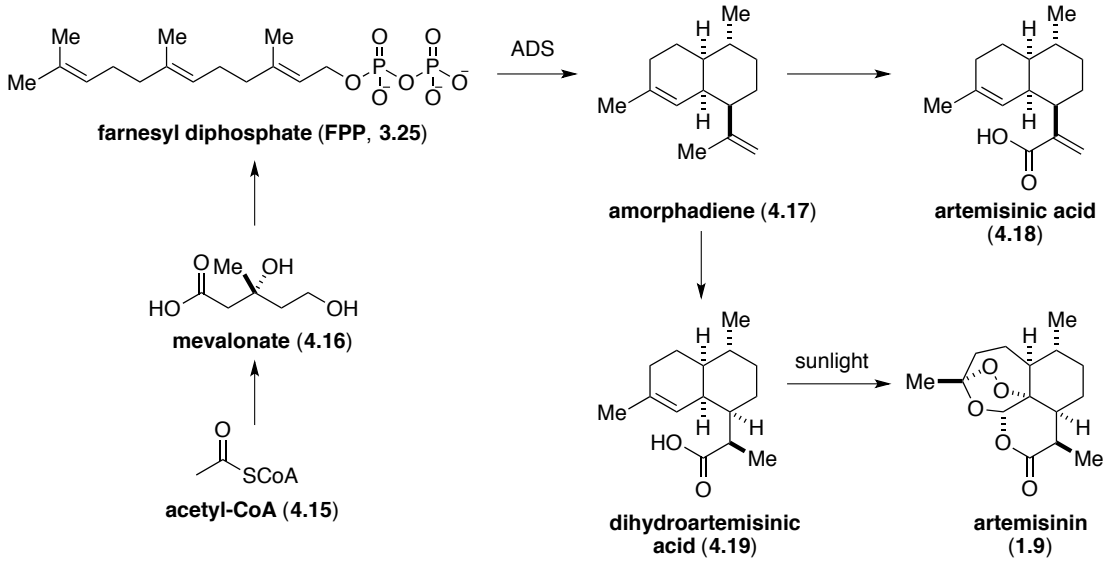


Scheme 4.2: Proposed radical-degradation pathway of artemisinin (**1.9**).

[248] a) S. Krishna, A.-C. Uhlemann, R. K. Haynes, *Drug Resist. Updat.* **2004**, *7*, 233; b) P. M. O'Neill, V. E. Barton, S. A. Ward, *Molecules* **2010**, *15*, 1705.

[249] D. J. Creek, E. Ryan, W. N. Charman, F. C. K. Chiu, R. J. Prankerd, J. L. Vennerstrom, S. A. Charman, *Antimicrob. Agents Chemother.* **2009**, *53*, 3496.

The biosyntheis[250] (Scheme 4.3) of artemisinin (**1.9**) starts from acetyl-CoA (**4.15**) *via* mevalonate (**4.16**) to farnesyl diphosphate (FPP, **3.25**). The enzyme amorphadiene synthase[251] (ADS) cyclizes FPP to amorphadiene (**4.17**). The bicyclic intermediate is then oxidized to either artemisinic acid (**4.18**) or dihydroartemisinic acid (**4.19**) in an enzymatic pathway.[252] The latter is then converted in a non-enzymatic fashion to artemisinin (**1.9**), *via* a sunlight driven photochemical[253] reaction using chlorophyll as photosensitizer.



Scheme 4.3: Biosynthesis of artemisinin (**1.9**).

Enantioselective total syntheses of artemisinin (**1.9**) had been reported[254] as well as a flow chemistry process[255] was developed. Scheme 4.4 shows the

[250] C. J. Paddon, J. D. Keasling, *Nat. Rev. Microbiol.* **2014**, *12*, 355.

[251] S. Picaud, P. Mercke, X. He, O. Sterner, M. Brodelius, D. E. Cane, P. E. Brodelius, *Arch. Biochem. Biophys.* **2006**, *448*, 150.

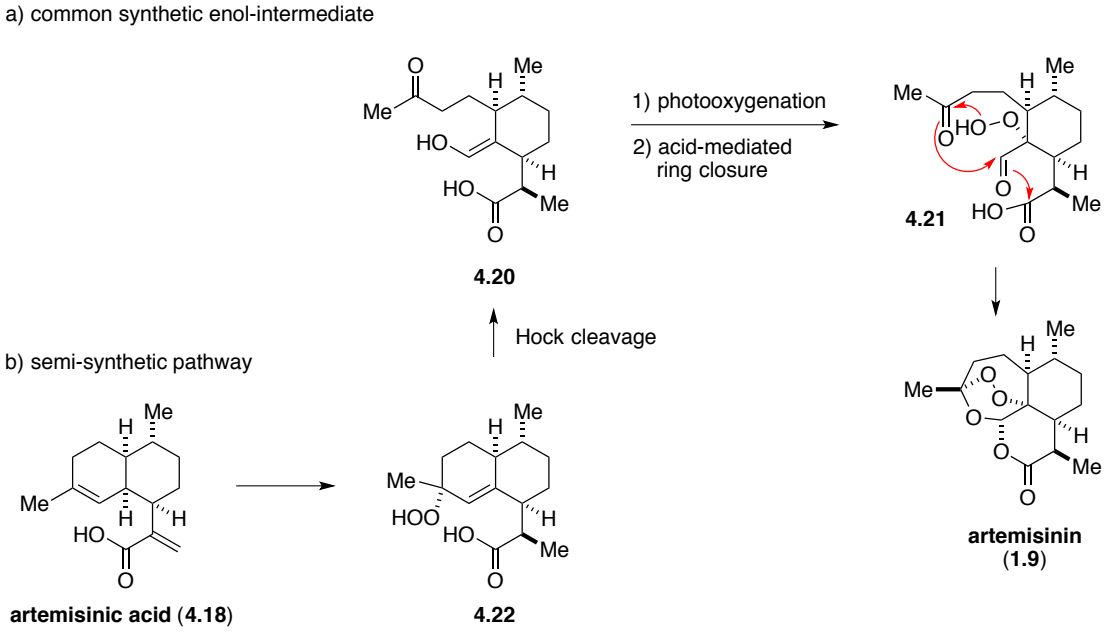
[252] M. E. Olsson, L. M. Olofsson, A.-L. Lindahl, A. Lundgren, M. Brodelius, P. E. Brodelius, *Phytochemistry* **2009**, *70*, 1123.

[253] G. D. Brown, *Molecules* **2010**, *15*, 7603.

[254] a) M. A. Avery, W. K. M. Chong, C. Jennings-White, *J. Am. Chem. Soc*. **1992**, *114*, 974; b) J. S. Yadav, R. S. Babu, G. Sabitha, *Tetrahedron Lett.* **2003**, *44*, 387; c) C. Zhu, S. P. Cook, *J. Am. Chem. Soc*. **2012**, *134*, 13577; d) J. S. Yadav, B. Thirupathaiah, P. Srihari, *Tetrahedron* **2010**, *66*, 2005; e) G. Schmid, W. Hofheinz, *J. Am. Chem. Soc*. **1983**, *105*, 624.

[255] F. Lévesque, P. H. Seeberger, *Angew. Chem. Int. Ed*. **2012**, *51*, 1706.

general strategy for the synthesis of artemisinin (**1.9**).[256] The enol **4.20** (Scheme 4.4a) undergoes first a photooxygenation to form the α-hydroperoxide **4.21**, which undergoes an acid-mediated ring closure to form artemisinin (**1.9**). A semi-synthetic pathway was elaborated (Scheme 4.4b) starting from artemisinic acid (**4.18**), which can be isolated from *Artemisia annua* in high amounts. Key transformation is a Hock cleavage[257] of the hydroperoxide **4.22** to enol **4.20** to form finally artemisinin (**1.9**).



Scheme 4.4: General established synthetic strategies for the synthesis of artemisinin (**1.9**).

4.1.5 Novel Endoperoxidal Antimalarial Scaffolds

Endoperoxides have shown to be remarkable antimalarial agents since the discovery of artemisinin (**1.9**). Artemisinin (**1.9**) SAR-studies led to even more potent antiplasmodial agents[258] and are recommended by the WHO for the treatment of malaria.[259] However, since it had been heavily used, the *Plasmodium* parasite developed widespread resistance against the drug.[226] Therefore, the research and development in the field of endoperoxide

[256] M. A. Corsello, N. K. Garg, *Nat. Prod. Rep*. **2015**, *32*, 359.

[257] a) J.-P. Lange, A. J. M. Breed, *Catal. Commun*. **2002**, *3*, 25; b) J. Brinkhorst, S. J. Nara, D. A. Pratt, *J. Am. Chem. Soc*. **2008**, *130*, 12224.

[258] D. Chaturvedi, A. Goswami, P. P. Saikia, N. C. Barua, P. G. Rao, *Chem. Soc. Rev*. **2010**, *39*, 435.

[259] Guidelines for the treatment of malaria, World Health Organization, Geneva, 2nd edn, **2010**.

structures is urgently needed. Novel molecular endoperoxidal scaffolds[260] (molecules **4.23** – **4.28**) are regarded as promising 2nd generation antimalarial agents and summarized in Figure 4.4.

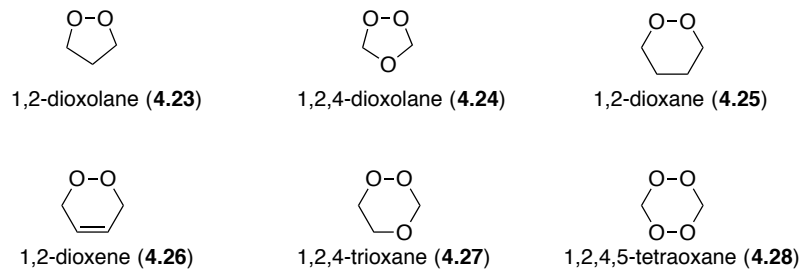


Figure 4.4: Endoperoxide scaffolds.

These newly investigated endoperoxidal scaffolds[236] have shown to be highly active in the sub-nanomolar range and showed good cytotoxic compatibility. OZ277 **4.29** and OZ439 **4.30** are promising candidates in clinical phases (Figure 4.5).[261] SAR-studies on OZ277 **4.29** led to the identification of OZ439 **4.30**. An improved pharmacokinetic effect was achieved by varying the side chain from an alkyl to an aryl group,[262] which led to a higher stability of the O-O bond towards Fe(II), probably due to steric reasons. *In vivo* test showed that a single dose of OZ439 **4.30** was sufficient for a total cure of malaria, whereas a single dose treatment using artemisinin was insufficient. RKA 182 **4.31** represents a tetraoxanescaffold.[263,264] This scaffold is superior to dioxolane in terms of stability and often activity.[265] CDRI-97/78 **4.32** consists of a trioxane moiety and clinical phase I tests are ongoing.[266]

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[260] A. O. Terent'ev, D. A. Borisov, V. A. Vil, V. M. Dembitsky, *Beilstein J. Org. Chem*. **2014**, *10*, 34.

[261] R. Brun, J. L. Vennerstrom *et al. J. Med. Chem*. **2010**, *53*, 481.

[262] L. Vennerstrom *et al., Proc. Natl. Acad. Sci*. **2011**, *108*, 4400.

[263] S. A. Ward *et al*., *Angew. Chem. Int. Ed*. **2010**, *49*, 5693.

[264] P. Ghorai, P. H. Dussault, *Org. Lett*. **2009**, *11*, 213.

[265] R. P. M. O'Neill *et al*., *J. Med. Chem*. **2008**, *51*, 2170.

[266] a) C. Singh, V. P. Verma, N. K. Naikade, A. S. Singh, M. Hassam, S. K. Puri, *J. Med. Chem*. **2008**, *51*, 7581; b) *Bioorg. Med. Chem. Lett*. **2010**, *20*, 4459; c) H. N. Kushwaha, N. Gautam, A. Misra, B. Singh, S. Kumar, H. H. Siddiqui, S. K. Singh, *Arzneimittelforschung* **2012**, *62*, 274.

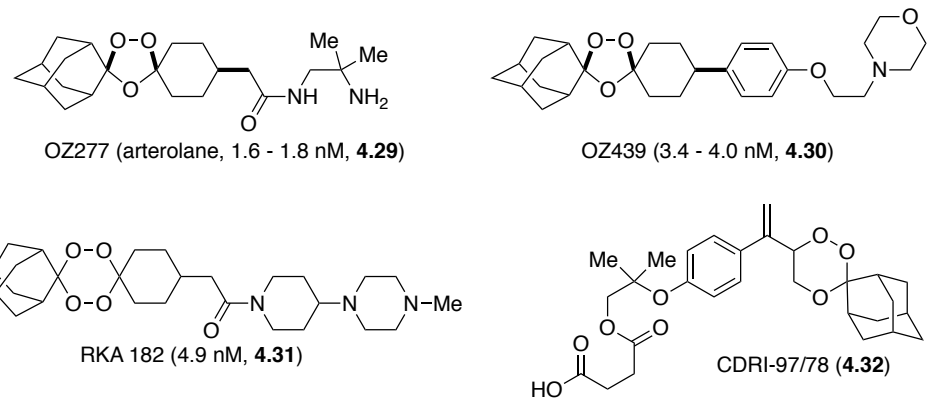
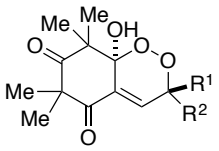


Figure 4.5: Scaffolds of novel antimalarial peroxides.

4.1.6 Natural Products Containing a 1,2-Dioxan-3-ol Scaffold – G-Factors

The G-factor series [267] (plant growth regulators**,** molecules **4.33** – **4.35**) were extensively studied by the group of Baltas and André-Barrès and their synthetic investigations as well as anitplasmodial activities are suggesting that 1,2-dioxane-3-ol motifs are valuable antiplasmodial agents. 1,2-Dioxane-3-ol has an additional free hydroxy function in position 3 on the common 1,2-dioxane scaffold. These antimalarial active natural products were isolated from *Eucalyptus grandis*[268] and their general structure is illustrated in Figure 4.6.



	R^1	R^2	
G1	Me	Et	(**4.33**)
G2	Et	Me	(**4.34**)
G3	Me	Me	(**4.35**)

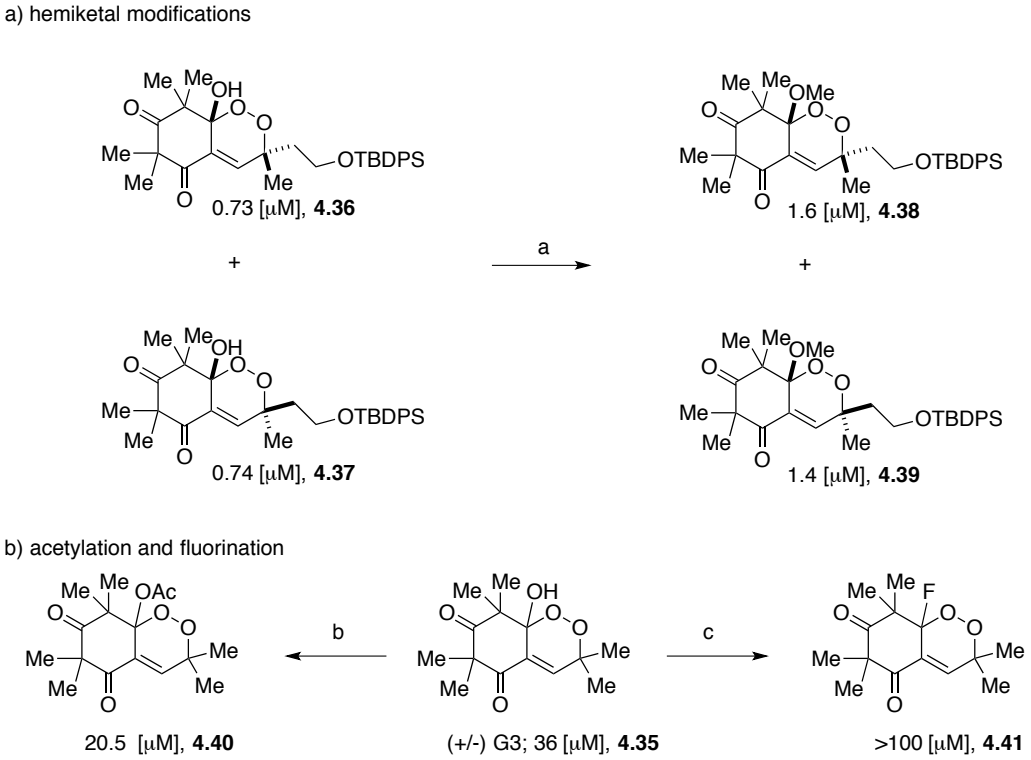
Figure 4.6: G-factor (G1 **4.33**, G2 **4.34**, G3[267a] **4.35**) series with the 1,2-dioxane-3-ol motif.

SAR-studies showed that modifications of the free hydroxy (**4.36** and **4.37**) to a hemiketal function (**4.38** and **4.39**) have minor influences on the

[267] a) M. Gavrilan, C. André-Barrès, M. Baltas, T. Tzedakis, L. Gorrichon, *Tetrahedron Lett*. **2001**, *42*, 2465; b) V. Bernat, C. André-Barrès, M. Baltas, N. Saffon, H. Vial, *Tetrahedron* **2008**, *64*, 9216.

[268] M. Baltas, M. Benbakkar, L. Gorrichon, C. Zedde, *Journal of Chromatography A* **1992**, *600*, 323.

antimalarial activity (Scheme 4.5a).[269] Further, it was found that the free hydroxy (G3, **4.35**) or either acetylated hydroxy function **4.40** is crucial for antiplasmodial activity (Scheme 4.5b).[270] Substitution of the free hydroxy group with to a fluorine **4.41** led to decreased anitplasmodial activity. The studies indicated that the G-factor series with the general 1,2-dioxane-3-ol scaffold itself are promising for future malaria treatment agents.



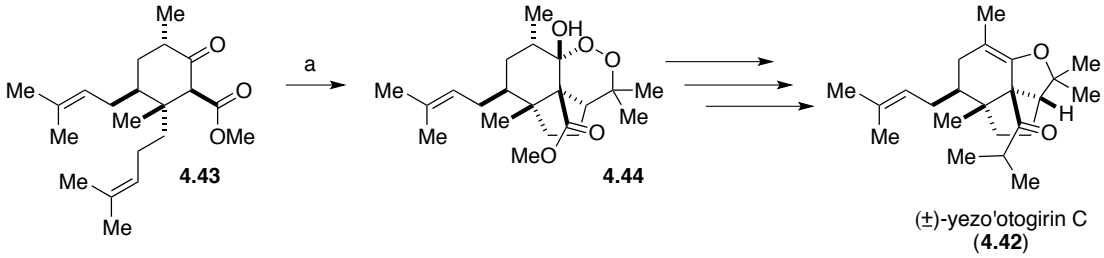
Scheme 4.5: Modified G-factors; values obtained from antiplasmodial tests[269-270] against the Nigerian strain of *Plasmodium falciparum*. a) *n*-BuLi, THF, −78 °C, 1 h, then MeOTf, −78 °C, 3 h, 83%; b) Ac_2O, Et_3N, CH_2Cl_2; c) DAST, 50%.

[269] a) C. Givelet, V. Bernat, M. Danel, C. André-Barrès, H. Vial, *Eur. J. Org. Chem*. **2007**, 3095; b) additional residues (morpholine, piperidine, *N*-heterocycles) were additionally tested but showed as well lower antisplamodial activity.

[270] F. Najjar, L. Gorrichon, M. Baltas, H. Vial, T. Tzedakis, C. André-Barrès, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1433.

4.1.7 Mn(III)-Catalyzed Approaches Towards 1,2-Dioxane-3-ol

The endoperoxide scaffold acts as a synthon of furans and are therefore often used as an intermediate in total syntheses.[271] In the protecting group free synthesis of (±)-yezo'otogirin C (**4.42**), Lee and co-workers applied an intramolecular manganese-mediated radical cyclization of a β-ketoester **4.43** with an olefin to reach the 1,2-dioxane-3-ol intermediate **4.44**.[272] After a tedious screening the bioinspired oxidative cyclization was achieved using Mn(II)/Mn(III) and oxygen (Kurosawa and Nishino's conditions).[273] The peroxide bridge was then reduced to afford the desired furane moiety and further manipulations yielded the desired natural product (±)-yezo'otogirin C (**4.42**) as shown in Scheme 4.6.



Scheme 4.6: Manganese mediated peroxide formation in Lee's total synthesis of (±)-yezo'otogirin C (**4.42**). a) $Mn(OAc)_2$ x 4 H_2O, $Mn(OAc)_3$ x 2 H_2O (cat.), O_2, EtOH, r.t., 2 d, 55%.

An impressive manganese–mediated radical peroxide bridge formation was reported by Gao and co-workers in their synthesis of the anticancer agent (+)-fusarisetin A (**4.45**, Scheme 4.7).[274] Their careful analysis of previously reported possible biosynthetic intermediates,[275] showed that equisetin

[271] a) H. H. Wassermann, J. L. Ives, *Tetrahedron* **1981**, *37*, 1825; b) B. Harichian, P. D. Magnus, *Synthetic Communications* **1977**, *7*, 119.

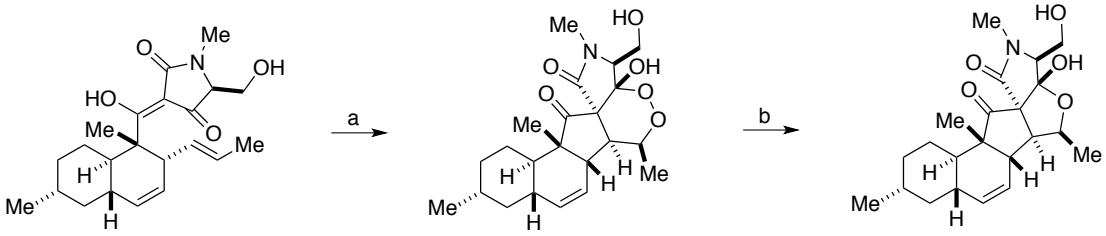
[272] S. He, W. Yang, L. Zhu, G. Du, C.-S. Lee, *Org. Lett*. **2014**, *16*, 496.

[273] C. Y. Qian, T. Yamada, H. Nishino, K. Kurosawa, *Bull. Chem. Soc. Jpn*. **1992**, *65*, 1371.

[274] a) J. Yin, C. Wang, L. Kong, S. Cai, S. Gao, *Angew. Chem. Int. Ed.* **2012**, *51*, 7786; b) J. Yin, S. Gao, *Synlett* **2014**, *25*, 1.

[275] J. W. Sims, J. P. Fillmore, D. D. Warner, E. W. Schmidt, *Chem. Commun*. **2005**, 186.

(**4.46**)[276] could act as a suitable precursor. Treating equisetin (**4.46**) in the presence of a catalytic amount of Mn(III)acetate and oxygen formed peroxyfusarisetin (**4.47**) *via* a formal [2 + 2 + 2] cycloaddition reaction. The natural product was obtained after reduction of the peroxide bridge with zinc to form (+)-fusarisetin A (**4.45**).



equisetin (**4.46**) peroxyfusarisetin (**4.47**) (+)-fusarisetin A (**4.45**)

Scheme 4.7: Gao's synthesis of (+)-fusarisetin A (**4.45**): a) $Mn(OAc)_3 \cdot 2\ H_2O$ (cat.), O_2, r.t., AcOH, 2 h; b) Zn, 50 °C, 2 h, 41% (over two steps).

4.2 Goal of this Study

In the course of our studies towards the natural product Striatal A (see chapter five of this thesis), we found an unexpected transformation in which a spontaneous reaction of an intermediate gave rise to a novel 1,2-dioxane-3-ol. Surprisingly, the reaction proceeded without the presence of any metal or solvent, solely air and sunlight was required for the transformation. In this study we aimed to elucidate the antimalarial activity of these novel endoperoxides and their derivatives. These possible new antimalarial agents would be readily available from inexpensive starting materials and provide a new lead compound for further antiplasmodial activity studies.

[276] H. R. Burmeister, G. A. Bennett, R. F. Vesonder, C. W. Hesseltine, *Antimicrob. Agents Chemother*. **1974**, *5*, 634; b) N. J. Phillips, J. T. Goodwin, A. Fraiman, R. J. Cole, D. G. Lynn*, J. Am. Chem. Soc*. **1989**, *111*, 822.

4.2.1 Synthesis of 1,2-Dioxane-3-ol *via* a Formal [2 + 2 + 2] Cycloaddition

The synthesis of the endoperoxides **4.48** and **4.49** commenced from commercially available enantiopure (*S*)-limonene (**4.50**) following a modified procedure from Wender and co-workers (Scheme 4.8).[277] The terminal olefin was regioselectively reduced to the methyl function and the trisubstituted olefin cleaved *via* an ozonolysis to yield the desired ketoaldehyde **4.51**. A Dieckmann condensation furnished the five-ring and the aldehyde was reduced to the allylic alcohol **4.52** using DIBAL-H. We were pleased to see that the Eschenmoser-Claisen rearrangement[278] was superior to the reported Claisen-rearrangement.[277] An improved diastereomeric ratio of 10:1 and 90% yield could be enhanced to a diastereomeric ratio of 24:1 and 95% yield for the formed amide **4.53** The inseparable diastereomeric amide mixture was then reduced [279] in the presence of 1,1,3,3-tetramethyldisiloxane in combination with $Ti(O^iPr)_4$ to the known aldehyde **4.54**[277] in 95% yield. Other reduction methods *via* an ate-complex,[280] DIBAL-piperidine complex[281] or triethoxyaluminumhydride[282] proved to be inefficient. Finally, the diketone **4.55** was obtained from a L-proline catalyzed Knoevenagel condensation and the obtained olefin was reduced *in situ* in the presence of Hantzsch ester. NMR-analysis showed the desired keto-enol products **4.55** along with a minor by-product. NMR-measurements over several days gave a clean formation of the keto-enol product **4.55** to the by-product, which was identified after intensive NMR, mass spectrometry and crystal structure analysis as a novel endoperoxidal scaffold **4.48** and **4.49**. Optimized conditions were found for

[277] P. A. Wender, F. C. Bi, M. A. Brodney, F. Gosselin, *Org. Lett*. **2001**, *3*, 2105.

[278] a) A. E. Wick, D. Felix, K. Steen, A. Eschenmoser, *Helv. Chim. Acta* **1964**, *47,* 2425; b) V. Bisai, R. Sarpong, *Org. Lett*. **2010**, *12*, 2551.

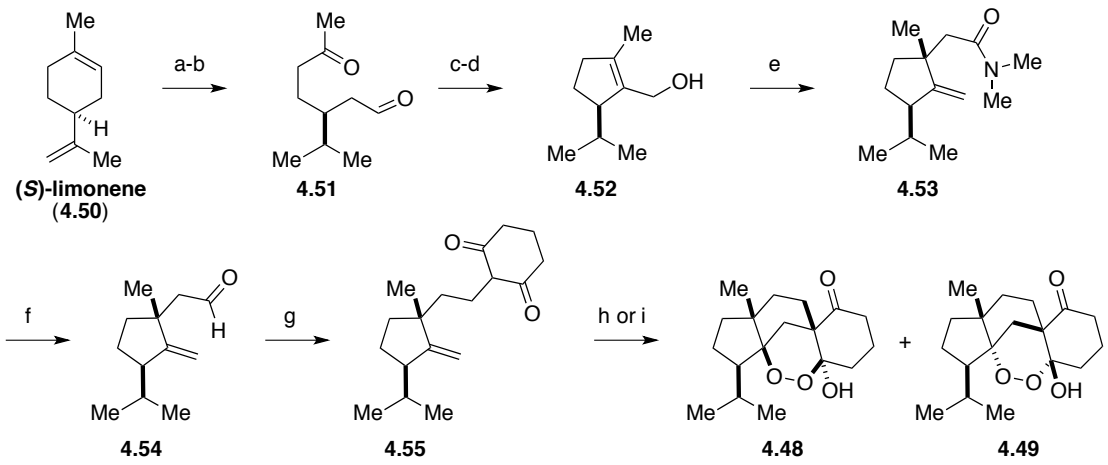
[279] a) S. Bower, K. A. Kreutzer, S. L. Buchwald, *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 1515; b) S. Laval, W. Dayoub, A. Favre-Reguillon, P. Demonchaux, G. Mignani, M. Lemaire, *Tetrahedron Lett*. **2010**, *51*, 2092.

[280] S. Kim, K. H. Ahn, *J. Org. Chem*. **1984**, *49*, 1717.

[281] S. M. Woo, M. E. Kim, D. K. An, *Bull. Korean Chem. Soc*. **2006**, *27*, 1913.

[282] H. C. Brown, A. Tsukamoto, *J. Am. Chem. Soc*. **1964**, *86*, 1089.

this unexpected conversion by treating the instable diketone **4.55** with oxygen in EtOAc to yield the endoperoxides **4.48** and **4.49** in 65% and a diastereomeric ratio of 5:1. The yield was even further increased to 97% using a catalytic amount of $Mn(OAc)_3$ in AcOH, which acts as a SET-transfer reagent.[272,274]



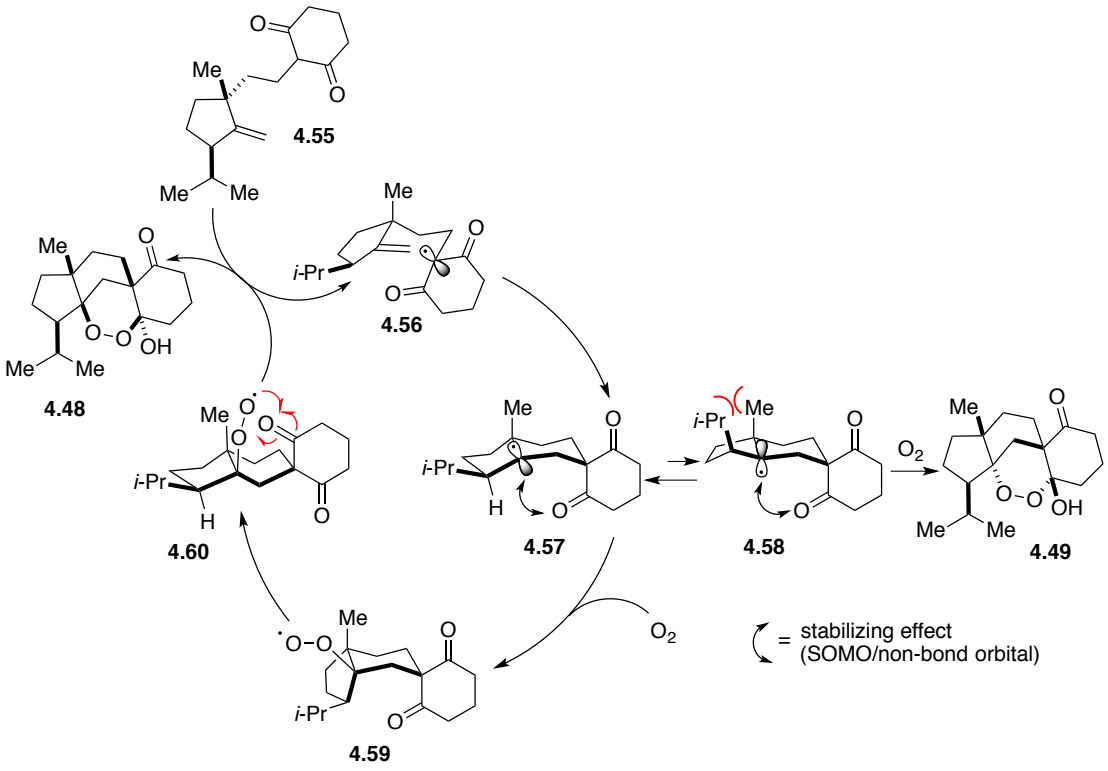
Scheme 4.8: Synthesis of endoperoxides **4.48** and **4.49**. a) H_2, PtO_2 (cat.), THF, r.t., 94%; b) O_3, Zn/AcOH, CH_2Cl_2/MeOH (5:1), −78 °C, 94%; c) piperidine, AcOH, benzene, 110 °C, 75%; d) DIBAL-H, Et_2O, 0 °C, 96%; e) 1,1-dimethoxyethyl(dimethyl)amine, *p*-xylene, 16 h, 150 °C, 95% (d.r. = 24:1); f) 1,1,3,3-tetramethyldisiloxane, $Ti(O^iPr)_4$, THF, r.t., 18 h, 95%; g) L-proline, Hanztsch ester, CH_2Cl_2, r.t., 19 h, 91%; h) hν, O_2, EtOAc, r.t., 16 h, 65%; i) AcOH, O_2, $Mn(OAc)_3$ (cat.), r.t., 19 h, 97%.

4.2.2 Mechanistic considerations

This unusual reaction can be regarded as a formal [2 + 2 + 2] cycloaddition and the use of this transformation was demonstrated by a variety of other groups.[283] We propose a formal [2 + 2 + 2] cycloaddition mechanism, which is

[283] a) T. Yamada, Y. Iwahara, H. Nishino, K. J. Kurosawa, *Chem. Soc., Perkin Trans. 1* **1993**, 609; b) S.-I Tategami, T. Yamada, T. H. Nishino, J. D. Korp, K. Kurosawa, *Tetrahedron Lett*. **1990**, *31*, 6371; c) R. Kumabe, H. Nishino, M. Yasutake, V.-H. Nguyen, K. Kurosawa, *Tetrahedron Lett*. **2001**, *42*, 69; d) R. Kumabe, H. Nishino, *Tetrahedron Lett*. **2004**, *45*, 703; e) K. Asahi, H. Nishino, *Tetrahedron* **2005**, *61*, 11107; f) K. Asahi, H. Nishino, *Eur. J. Org. Chem*. **2008**, *2008*, 2404; g) M. Persico, A. Quintavalla, F. Rondinelli, C. Trombini, M. Lombardo, C. Fattorusso, V. Azzarito, D. Taramelli, S. Parapini, Y. Corbett, G. Chianese, E. Fattorusso, O. Taglialatela-Scafati, *J. Med. Chem*. **2011**, *54*, 8526; h) G. Majetich, G. Zou, S. Hu, *Org. Lett*. **2013**, *15*, 4924.

initiated by an autooxidation[284] to give the α-keto-radical **4.56** of the diketone **4.55** as depicted in Scheme 4.9. A 6-*endo*-*trig* cyclization with the terminal double bond gives the tricyclic framework with a *C*-centered tertiary radical species **4.57** or **4.58**. The diastereoselectivity can be explained by the hybridization of the tertiary radicals **4.57** and **4.58**, where latter is less favored due to a 1,3-steric interaction of the methyl and isopropyl residue. Furthermore, a *trans*-[4.3.0]nonane framework is less preferred than the *cis*-analogue. In addition, the intermediate **4.57** may have a better orbital overlap between the SOMO and the non-bonding orbital of the carbonyl function, than intermediate **4.58**, which gives further a stabilizing effect. Addition of O_2 to either **4.57** or **4.58** forms the peroxyradical intermediate **4.59** (only the major diastereomer pathway is shown). Upon ring flip, cyclization with the carbonyl function of **4.60** yields in the major endoperoxide diastereomer **4.48**.



Scheme 4.9: Proposed mechanism for the endoperoxide formation.

[284] a) G.-W. Wang, Q.-Q. Lu, J.-J. Xia, *Eur. J. Org. Chem*. **2011**, *2011*, 4429; b) V. Bernat, M. Coste, C. André-Barrès, *New J. Chem*. **2009**, *33*, 2380.

We further investigated on the proposed mechanism by adding the radical inhibitor BHT to the reaction mixture and indeed no endoperoxide product could be observed. Unfortunately, radical trapping experiments with TEMPO failed and only decomposition of the starting material could be observed. The intramolecular radical addition and steric effects of the condensed molecular scaffold might not allow a radical trapping with TEMPO.

4.2.3 SAR-studies and Antiplasmodial Activity

An initial antiplasmodial activity test of the endoperoxides **4.48** and **4.49** on the parasite *Plasmodium falciparum* showed promising IC_{50}-values in the nanomolar range as well as low cytotoxicity values (rat myoblast L6 cells). We then further elucidated the activity dependency of the C-3 functionality and therefore synthesized derivatives of the parent compound (Scheme 4.10).[285] *O*-Methylation under standard methylation conditions (*p*-TsOH/MeOH) were not suitable due to low and incomplete conversion. Applying Irvine-Purdie conditions[286] using Ag_2O and MeI furnished the methylated endoperoxide acetals **4.61** and **4.62** in reasonable yields (88%, 54%). Both structures were secured by crystals structure analysis. Similar problems were observed for the acetoxy formation. Standard conditions (Ac_2O/DMAP in Et_3N or py)[287] showed slow conversion towards the desired compounds **4.63** and **4.64**. Satisfyingly the non-nucleophilic Barton's base **4.65**[288] furnished the desired acetoxy compound **4.63** in 76% yield. Surprisingly, the reacation did not proceed with diastereomer **4.64**, probably due to steric hindrance of the densed molecule.

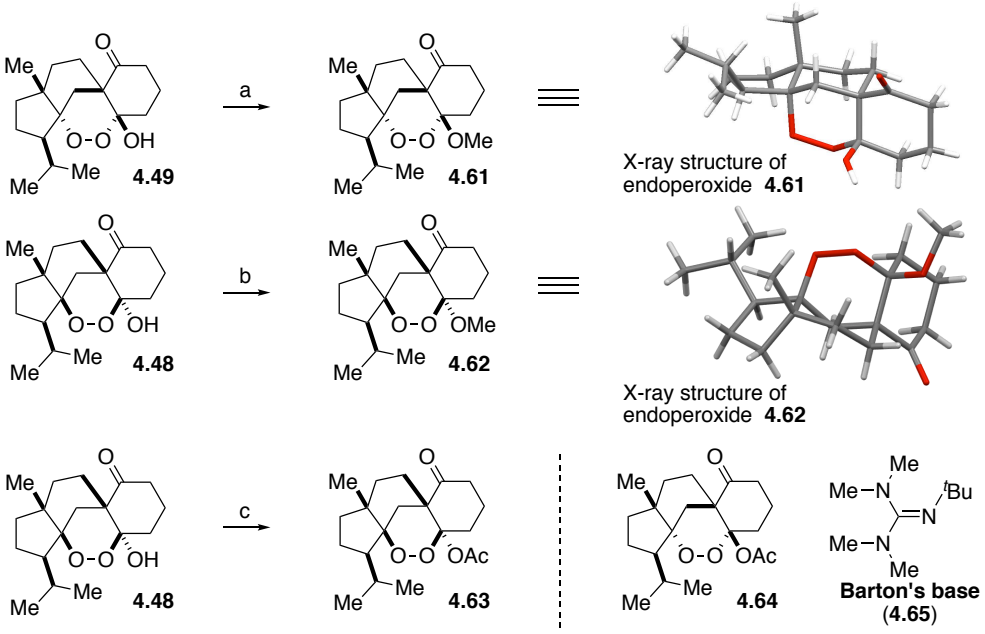
---

[285] a) G. Chianese, E. Fattorusso, F. Scala, R. Teta, B. Calcinai, G. Bavestrello, H. A. Dien, M. Kaiser, D. Tasdemir, O. Taglialatela-Scafati, *Org. Biomol. Chem*. **2012**, *10*, 7197; b) F. Najjar, M. Baltas, L. Gorrichon, Y. Moreno, T. Tzedakis, H. Vial, C. André-Barrès, *Eur. J. Org. Chem*. **2003**, *2003*, 3335.

[286] V. Thornqvist, S. Manner, O. F. Wendt, T. Frejd, *Tetrahedron* **2006**, *62*, 11793.

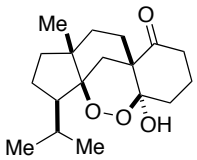
[287] a) J.-F. Berrien, O. Provot, J. Mayrargue, M. Coquillay, L. Ciceŕon, F. Gay, M. Danis, A. Robert, B. Meunier, *Org. Biomol. Chem*. **2003**, *1*, 2859; b) F. Najjar, L. Gorrichon, M. Baltas, H. Vial, T. Tzedakis, C. Andreź-Barreś, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 143; c) K. Asahi, H. Nishino, *Tetrahedron* **2005**, *61*, 11107.

[288] D. H. R. Barton, J. D. Elliott, S. D. J. Géro, *Chem. Soc., Perkin Trans. 1* **1982**, 2085.

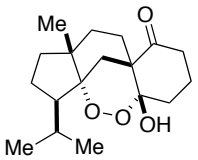


Scheme 4.10: Synthesis of endoperoxide derivatives for SAR-studies (X-ray structure color code: grey = carbon; red = oxygen; white = hydrogen). a) Ag_2O, MeI, ACN, 40 °C, 16 h, 88%; b) Ag_2O, MeI, ACN, 40 °C, 16 h, 54%; c) Barton's base, Ac_2O, DMAP, CH_2Cl_2, r.t., 20 h, 76%.

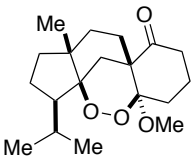
The activity of the synthesized derivatives were tested in collaboration with Dr. Marcel Kaiser form the Swiss Tropical and Public Health Institute (see experimental part of this thesis for further information). The activity of the tested endoperoxides ranged from the submicromolar to nanomolar range (Table 4.1). Compound **4.48** (entry 2) was by far the most active endoperoxide with a good antiplasmodial activity of 180 nM, a cytotoxicity value of 169 and an excellent selectivity index of 939. The study showed clearly that the free hydroxyperoxide is crucial for the activity and further modifications of this group decreased its potency significantly (entries 3-5). This is in contrast to other published works, where substitution on the free hydroxyl group led to an increased activity by a factor of 10.[285-286] The major diastereomeric analogue **4.48** (entry 1) is almost 40 times less active than the minor diastereomer **4.49** (entry 2). The same activity trend is also present in their methylated analogues **4.62** and **4.61** (entry 3 and 4) as well as for the acetylated compound **4.63** (entry 5). An unfavored steric interaction of the methyl and isopropyl moieties could shield the endoperoxide interaction to the Fe(II)-heme-cluster and yield in a decreased activity.



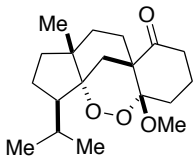
4.48



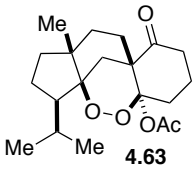
4.49



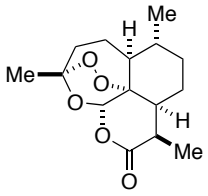
4.62



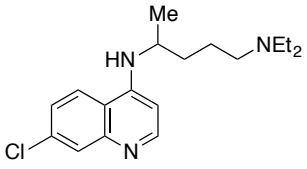
4.61



4.63



artemisninin (**1.9**)



chloroquine (**4.6**)

entry	compound	IC_{50} [μM][a]	LD_{50} [μM][b]	SI[c]
1	**4.48**	7.1	165	23
2	**4.49**	0.18	169	939
3	**4.62**	24.3	59	2
4	**4.61**	3	175	58
5	**4.63**	32.2	168	5
6	artemisinin (**1.9**)[d]	0.0035	349	98500
7	chloroquine (**4.6**)[d]	0.0063	107	17145

Table 4.1: Antiplasmodial activity and cytotoxicity screening. [a]*Plasmodium falciparum* NF54 strain; [b]rat myoblast L6 cells; [c]Selectivity index (SI) = LD_{50}/IC_{50}; [d]artemisinin (**1.9**) and chloroquine (**4.6**) were additionally tested for confirmation reasons.

4.3 Conclusion

A serendipitous observation led to the discovery of a transformation leading to novel endoperoxide based antimalarial agents. In this reaction, a diketone moiety **4.55** underwent a spontaneous formal [2 + 2 + 2] cycloaddition onto a terminal olefin in the presence of oxygen to give a 1,2-dioxane-3-ol skeleton. This radical reaction could be further improved by the addition of a catalytic amount of manganese(III)acetate in the presence of oxygen. *In vivo* assays of the novel endoperoxides **4.48** and **4.49** and their hemiacetal derivatives **4.61** – **4.63** on the malaria parasite *Plasmodium falciparum* showed submicromolar to nanomolar activity and good to excellent cytotoxicity values for the 1,2-dioxane-3-ol's (IC_{50} = 180 nM activity, LD_{50} = 169 μM, SI = 939). The free hydroxy-endoperoxide function is crucial for antiplasmodial activity and steric interactions around the endoperoxide scaffold yielded in a decreased activity.

5 Synthetic Studies Towards the Natural Product Striatal A

5.1 Fungal Natural Products – A Sustainable Source of Novel Drug Leads

Finding effective therapeutic options for combatting serious diseases such as cancer, AIDS or malaria is a continuous challenge for natural scientists. Nature's inestimable biodiversity on earth is interdependently correlated to an immense treasure trove of natural products. Representatives of all six kingdoms of life[289] (animals, plants, fungi, archaea, bacteria and protista) produce a vast diversity of structurally complex natural products that have very often served as a starting point for the development of novel pharmaceuticals and for the discovery of new modes of biological action. Up to date, most of these lead structures have been based on natural products isolated from bacteria and plants. Natural products derived from fungi have so far played a minor role for drug development, although fungi are known to produce a great variety of secondary metabolites and may thus provide novel scaffolds for medicinal chemistry.[290] Fungal-derived pharmaceuticals have already shown their potential as effective drugs or precursors thereof (Figure 5.1): *Penicillium chrysogenum* produces the antibacterial agent penicillin G (**1.1**) with its characteristic β-lactam structure. It was discovered by Sir Alexander Fleming in 1928 and inhibits the cell wall biosynthesis of bacteria.[291] The immunosuppressive cyclosporin A (**5.1**), isolated from the fungus *Tolypocladium inflatum*,[292] prevents graft rejection following organ

[289] An updated classification of living organisms see: T. Cavalier-Smith, *Biol. Rev*. **1998**, *73*, 203; for an older classification see: R. H. Whittaker, *Science* **1969**, *163*, 150.

[290] S. P. Wasser, A. L. Weiss, *International Journal of Medicinal Mushrooms* **1999**, *1*, 31.

[291] a) K. Lewis, *Nat. Rev. Drug Discov*. **2013**, *12*, 371; b) A. Fleming, *Br. J. Exp. Pathol*. **1929**, *10*, 226.

[292] H. Svarstad, H. C. Bugge, S. S. Dhillon, *Biodiversity and Conservation* **2000**, *9*, 1521.

transplantation by inhibiting indirectly the enzyme calcinerum.[293] Overall, T-cells activation is inhibited, which leads to a much higher survival rate of operated patients. Echinocandin B (**5.2**) was isolated from *Aspergillus nidulans var. echinulatus* in 1974.[294] This large lipopeptide inhibits the enzyme 1,3-β-d-glucan synthase (glucan synthesis), a component of the fungal cell.[295] Lovastatin (**5.3**) was isolated from a fermentation of *Aspergillus terreus*.[296] As all other statins, lovastatin inhibits the enzyme HMG-CoA reductase, which is responsible for cholesterol synthesis. Therefore the cholesterol and cholesterol accumulation is reduced in the blood and yields to a reduced development of arteriosclerosis and cardiovascular diseases.[297]

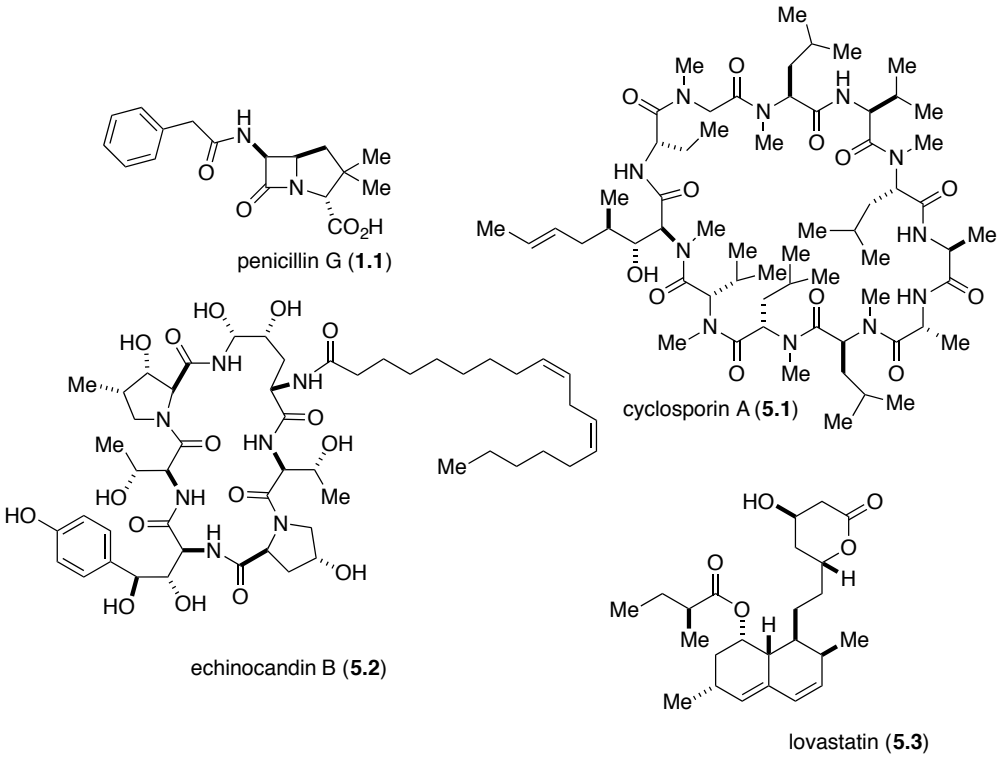


Figure 5.1: Fungal-derived pharmaceuticals.

[293] S. L. Schreiber, G. R. Crabtree, *Immunol. Today* **1992**, *13*, 136.

[294] F. Benz, F. Knüssel, J. Nüesch, H. Treichler, W. Voser, R. Nyfeler, W. Keller-Schierlein, *Helv. Chim. Acta* **1974**, *57*, 2459.

[295] D. W. Denning, *Lancet* **2003**, *362*, 1142.

[296] A. W. Alberts, J. Chen, G. Kuron, V. Hunt, J. Huff, C. Hoffman, J. Rothrock, M. Lopez, H. Joshua, E. Harris, A. Patchett, R. Monaghan, S. Currie, E. Stapley, G. Albers-Schonberg, O. Hensens, J. Hirshfield, K. Hoogsteen, J. Liesch, J. Springer, *Proc. Natl Acad. Sci.* **1980**, *77*, 3957.

[297] J. A. Tobert, *Nat. Rev. Drug Discov.* **2003**, *2*, 517.

A common strategy in the development of novel drugs is the chemical modification of natural product lead structures in order to improve their pharmacokinetic properties and simplify routes for the synthetic preparation of these agents.[298] The uncommon α-amino acid myriocin (**5.4**) has been isolated from the fungus *Isaria sinclairii* and shown to act as an antibiotic by inhibition of sphingosine biosynthesis.[299] Fingolimod (**5.5**), a truncated version of myriocin (**5.4**) has been prepared, which has been shown to be an immunomodulating agent effective in the treatment of multiple sclerosis (Figure 5.2). Acting as an agonist on four of five sphingosine-1-phosphate receptors,[300, 301] thus inhibits further infiltration of auto-aggressive lymphocytes, which causes inflammation by myelin sheath degeneration.[302] Furthermore, positive effects of fingolimod (**5.5**) on neuronal cell development have been reported.[303]

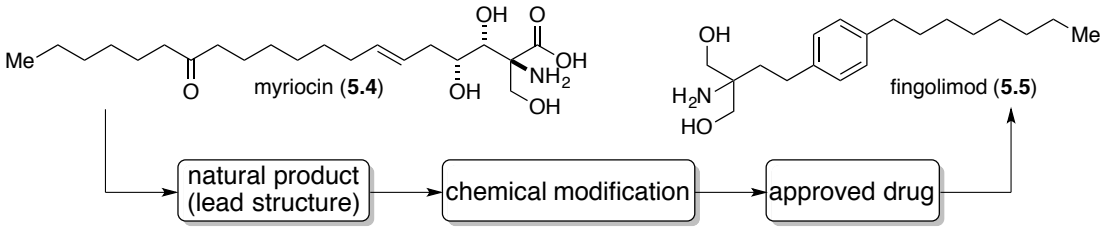


Figure 5.2: From lead structure to approved drug.

[298] a) E. A. Crane, K. Gademann, *Angew. Chem. Int. Ed*. **2016**, *55*, 2; b) T. Fujita, K. Inoue, S. Yamamoto, T. Ikumoto, S. Sasaki, R. Toyama, M. Yoneta, K. Chiba, Y. Hoshino and T. Okumoto, *J. Antibiot*. **1994**, *47*, 216.

[299] Y. Miyake, Y. Kozutsumi, S. Nakamura, T. Fujita, T. Kawasaki, *Biochem. Biophys. Res. Commun*. **1995**, *211*, 396.

[300] a) C. S. Garris, L. Wu, S. Acharya, A. Arac, V. A. Blaho, Y. Huang, B. S. Moon, R. C. Axtell, P. P. Ho, G. K. Steinberg, D. B. Lewis, R. A. Sobel, D. K. Han, L. Steinman, M. P. Snyder, T. Hla, M. H. Han, *Nat. Immunol.* **2013**, *14*, 1166; b) N. Sharma, A. S. Akhade, A. Qadri, *J. Leukoc. Biol*. **2013**, *93*, 521; c) S. Spiegel, S. Milstein, *Nat. Rev. Mol. Cell Biol.* **2003**, *4*, 397; d) H. Rosen, P. J. Gonzalez-Cabrera, M. Germana Sanna, S. Brown, *Annu. Rev. Biochem.* **2009**, *78*, 743.

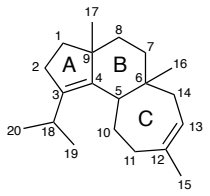
[301] J. Chun and H.-P. Hartung, *Clin. Neuropharmacol*. **2010**, *33*, 91.

[302] A. Bauer, M. Brönstrup, *Nat. Prod. Rep*. **2014**, *31*, 35.

[303] J. Ingwersen, O. Aktas, P. Kuery, B. Kieseier, A. Boyko, H.-P. Hartung, *Clin. Immunol.* **2012**, *142*, 15.

5.2 Cyathane Diterpenoids Natural Products and Their Biological Activities

Around 105 members of the cyathane diterpenoid natural product family are described.[304] The main characteristic of the cyathane family of diterpenoid natural products is the fused tricyclic 5-6-7 ring system with angular methyl groups at C-6 and C-9 (**5.6**, Figure 5.3).[305] The relative configuration of these two methyl groups is *anti* in all cyathane natural products except for cyanthiwigin type structures, where these two methyl groups are found to be in a *syn* relationship. Within the cyathane family, several subtypes of natural products have already been isolated and their biological activity will be discussed in full detail in this section. The most prominent natural products of this family have already been prepared by total syntheses, which will be discussed in full detail in chapter 5.4 of this thesis.[306]



5.6

Figure 5.3: Cyathane skeleton numbering and ring labeling.

[304] A review on cyathane structures: H.-Y. Tang, X. Yin, C.-C. Zhang, Q. Jia, J.-M. Gao, *Current Medicinal Chemistry* **2015**, *22*, 2375.

[305] An introduction to the family of cyathane natural products: D. L. Wright, C. R. Whitehead, *Org. Prep. Proced. Int*. **2000**, *32*, 309.

[306] Review about cyathane total syntheses: J. A. Enquist, Jr., B. M. Stoltz, *Nat. Prod. Rep*. **2009**, *26*, 661.

5.2.1 Cyathins and Cyafrins

In 1971, Ayer and co-workers isolated a novel natural product scaffold from the bird's nest fungus *Cyathus helenae*[307] and successfully elucidated the structure of cyathin A_3[308] (**5.7**) and allocyathin B_3[309] (**5.8**, Figure 5.4a).[310] The nomenclature of the C20 diterpenoids is based on the grade of unsaturation. Diterpenoid structures consist of 30 hydrogen atoms in their molecular formula are called cyathin A (**5.7** and **5.9**), those with only 28 hydrogen atoms are named cyathin B (**5.8** and **5.10**) and cyathin C (**5.11** and **5.12**) only contains 26 hydrogen atoms. The subscript numbers after the letter is referred to the amount of oxygens inside the molecule. The prefixes *allo*- or *neoallo such as* neoallocyathin A_4 *(***5.13**) are isomeric forms inside the cyathane family. The same nomenclature is applied on the closely related cyafrin family (**5.14** – **5.17**). The structural identification was rather complex due to the presence of a ketone-hemiketal equilibrium (**5.18** and **5.19**, Figure 5.4b).[305] These molecules are of particular interest due to their broad range of biological activity such as anti-inflammatory, antimicrobial and NGF-stimulating properties.

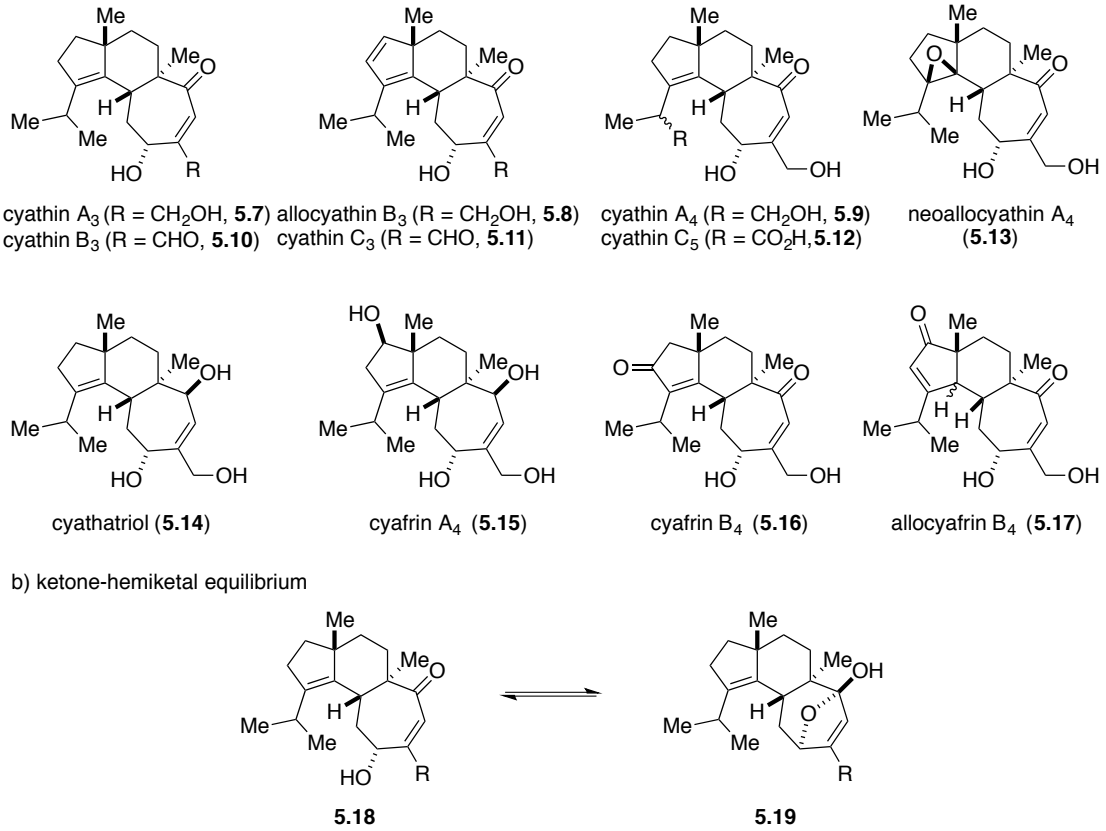
[307] a) A. D. Allbutt, W. A. Ayer, H. J. Brodie, B. N. Johri, H. Taube, *Can. J. Microbiol*. **1971**, *17*, 1401; b) W. A. Ayer, H. Taube, *Can. J. Chem*. **1973**, *51*, 3842.

[308] D. E. Ward, J. Shen, *Org. Lett*. **2007**, *9*, 2843.

[309] D. E. Ward, Y. Gai, Q. Qiao, *Org. Lett*. **2000**, *2*, 2125.

[310] W. A. Ayer, H. Taube*, Tetrahedron Lett*. **1972**, *13*, 1917.

a) cyathin and cyafrin natural products



b) ketone-hemiketal equilibrium

5.18 **5.19**

Figure 5.4: Cyathin and cyafrin structures.

5.2.2 Sarcodonins and Scabronines

The first members of the sarcodonin family sarcodonin A (**5.20**) and sarcodonin G[311] (**5.21**) were isolated from the fruiting body of the mushroom *Sarcodon scabrosus* by Shibata and co-workers in 1989.[312] Various other derivatives were discovered soon after (Figure 5.5a and 5.5c).[313] The scabronines were isolated from the same mushroom source and the natural products scabronine B (**5.22**), scabronine E (**5.23**) and scabronine F (**5.24**) have been found to stimulate the NGF synthesis.[314] The high potential of scabronines to treat neurological disorders has spurned extensive SAR-

[311] Total synthesis of sarcodonin G: a) E. Piers, M. Gilbert and K. L. Cook, *Org. Lett*. **2000**, *2*, 1407; b) S. P. Waters, Y. Tian, Y.-M. Li and S. J. Danishefsky, *J. Am. Chem. Soc*., **2005**, *127*, 13514.

[312] H. Shibata, T. Tokunaga, D. Karasawa, A. Hirota, M. Nakayama, H. Nozaki, T. Tada, *Agric. Biol. Chem*. **1989**, *53*, 3373.

[313] B.-J. Ma, J.-K. Liu, *J. Basic. Microbiol*. **2005**, *45*, 328.

[314] T. Kita, Y. Takaya, Y. O. Tomihisa, *Tetrahedron* **1998**, *54*, 11877.

studies as shown in Figure 5.5b and 5.5d (represented by structures **5.25** respectively **5.26**).[304] The unsaturation in the seven-membered ring is for the sarcodonin and scabronine family crucial for the activity. Furthermore, installation of a methylester group gave an increased activity.

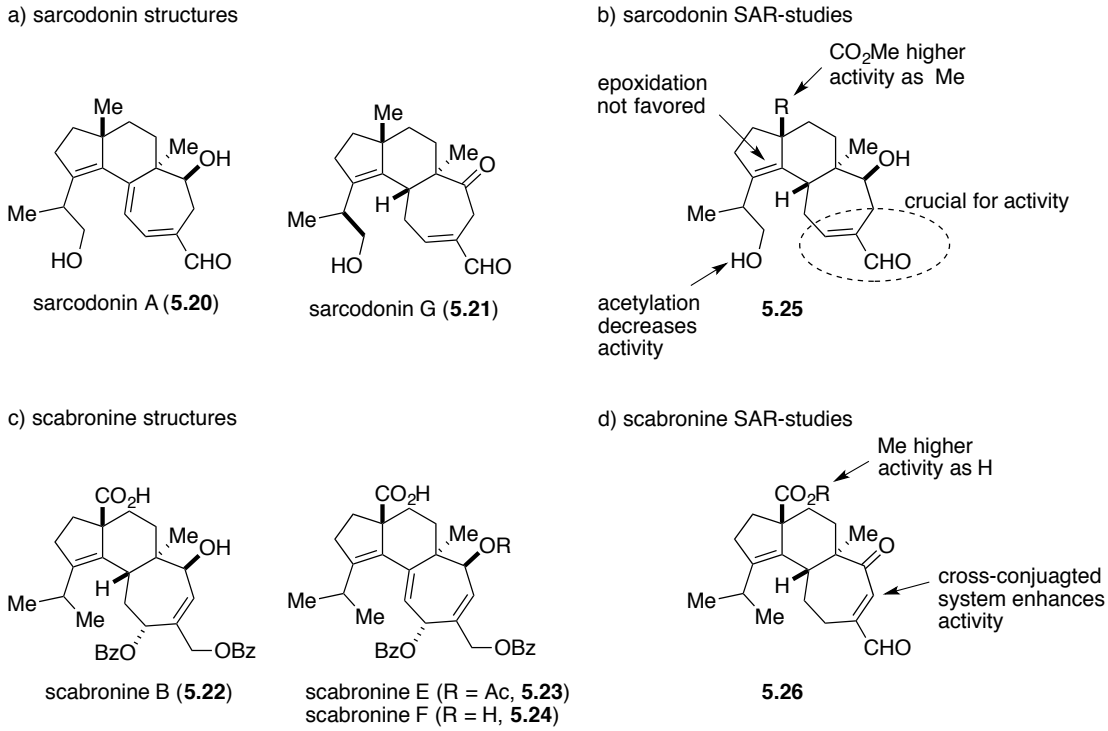


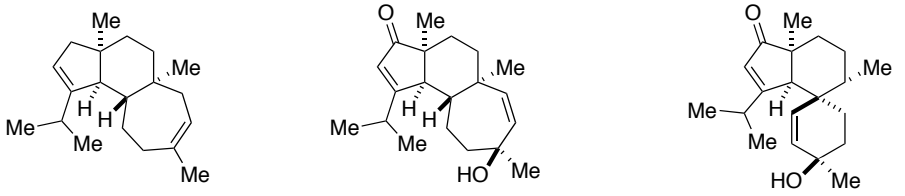
Figure 5.5: Representative sarcodonin and scabronine structures (left) and SAR-studies on their scaffold (right).

5.2.3 Cyanthiwigins

The biological source for the cyathane family of natural products are fungi, whereas the cyanthiwigins were isolated from marine sponges. Initially discovered by Kashman and co-workers in extracts from the marine sponge *Epipolasis reiswigi* and later by the group of Hammann from the Jamaican sponge *Myrmekioderma styx*, over 30 compounds of the cyanthiwigin family have been isolated.[315] All congeners feature two angular methyl groups at C-6 and C-9 in a *syn*-relationship to each other instead of an *anti*-configuration as common for cyathane structures. This hints at different terpene cyclases

[315] a) D. Green, I. Goldberg, Z. Stein, M. Ilan, Y. Kashman, *Nat. Prod. Lett*. **1992**, *1*, 193; b) J. Peng, K. Walsh, I. A. Weedman Braude, M. Kelly, M. T. Hamann, *Tetrahedron* **2002**, *58*, 7809; c) J. Peng, M. A. Avery, M. T. Hamann, *Org. Lett*. **2003**, *5*, 4575.

being involved in the biosyntheses of these two classes of natural products. The biological activity of cyanthiwigins ranges from antimicrobial and cytotoxic activity to the stimulation of neurite outgrowth. Due to their biological significance, total syntheses of the cyanthiwigin compounds (**5.27** – **5.29**) shown in Figure 5.6 had been reported by several groups.[316]



cyanthiwigin F (**5.27**) cyanthiwigin U (**5.28**) cyanthiwigin AC (**5.29**)

Figure 5.6: Cyanthiwigin members whose total synthesis has already been reported in literature.

5.2.4 Glaucopines and Cyrneines

The glaucopine and cyrneine families of natural products were discovered in the late 2000's. They represent a new class of cyathane diterpenoids (Figure 5.7a). Glaucopine A (**5.30**), glaucopine B [317] (**5.31**) and later glaucopine C [318] (**5.32**) were isolated from the fruiting body of *Sarcodon glaucopus* and were shown to have anti-inflammatory activity. The cyrneine family was isolated from the mushroom *Sarcodon cyrneus* and promotes neurite outgrowth (selected structures are shown in Figure 5.7a). Cyrneine B[319] (**5.33**) induced the highest level of NGF gene expression (factor 7.3), whereas cyrneine C (**5.34**) and cyrneine D[320] (**5.35**) were significantly less

[316] a) M. W. B. Pfeiffer, A. J. Phillips, *J. Am. Chem. Soc*. **2005**, *127*, 5334; b) T. J. Reddy, G. Bordeau, L. Trimble, *Org. Lett*. **2006**, *8*, 5585; c) J. A. Enquist, Jr., B. M. Stoltz, *Nature* **2008**, *453*, 1228.

[317] M. Curini, F. Maltese, M. C. Marcotullio, L. Menghini, R. Pagiotti, O. Rosati, G. Altinier, A. Tubaro, *Planta Med*. **2005**, *71*, 194.

[318] M. C. Marcotullio, R. Pagiotti, V. Campagna, F. Maltese, G. Fardella, G. Altinier, A. Tubaro, *Nat. Prod. Res.* **2006**, *20*, 917.

[319] M. C. Marcotullio, R. Pagiott, F. Maltese, Y. Obara, T. Hoshino, N. Nakahata, M. Curini, *Planta Med*. **2006**, *72*, 819.

[320] M. C. Marcotullio, R. Pagiott, F. Maltese, G. N. Oball-Mond Mwankie, T. Hoshino, Y. Obara, N. Nakahata, *Bioorg. Med. Chem.* **2007**, *15*, 2878.

active (factor 2.7 and 1.3, respectively) compared to no drug treatment in a PC12 cell assay. SAR-studies indicated that the α,β-unsaturated aldehyde is the most important structural feature for their biological activity (**5.36**, Figure 5.7b). Incorporation of a tertiary alcohol at the point of five and six ring fusion showed an increased activity. Furthermore, a secondary alcohol is preferred over ketone functionality on the seven-ring. Modification on the five ring has only minor effects on the activity.

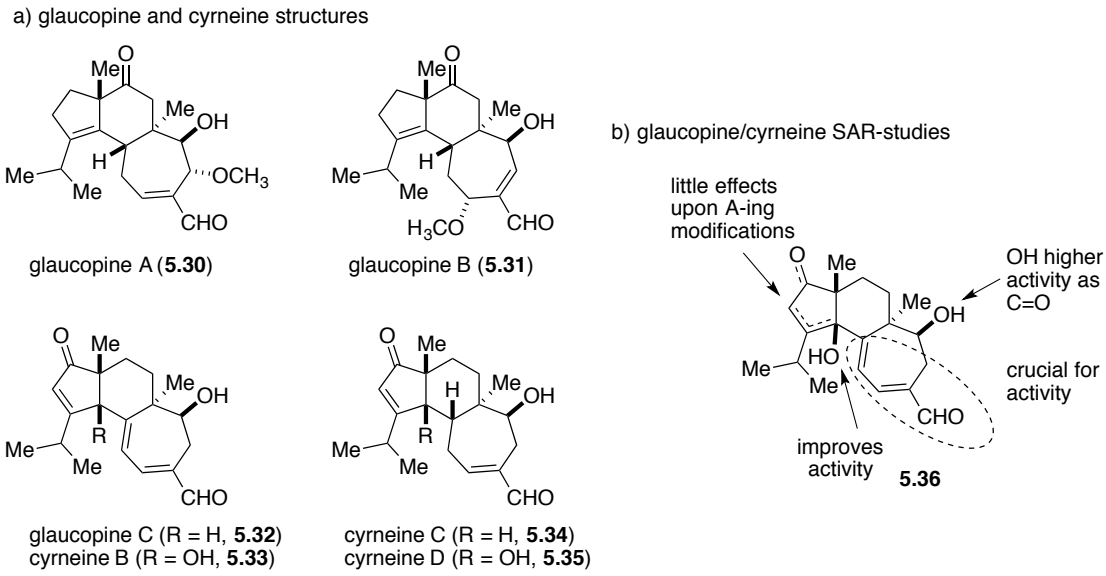


Figure 5.7: Selected members of the glaucopine and cyrneine family of natural products (left) and results from SAR studies (right).

5.2.5 Cyathane-Xylosides

Some of the cyathane scaffolds are attached to one or various pentose units and are thus called cyathane-xylosides. These pentose substituents are connected to the core of the molecule *via* glycosidic bonds. Cyathane-xyloside can either contain one or more pentose substituents and the sugars can have different oxidation patterns.

5.2.5.1 Striatoids and Laxitextines

Striatoids [321] and laxitextines [322] are cyathane-xylosides that have only recently been discovered (Figure 5.8). The group of Gao isolated striatoid structures (represented by structures **5.37** – **5.39**) from the fungus *Cyathus striatus.* Striatoid B (**5.38**) and some other congeners consist of a characteristic C-15 and C-4′ ether ring system. All newly isolated striatoid promote neurite outgrowth in combination with NGF in the PC12 cell assay. The laxitextines (represented by structures **5.40** – **5.41**) are the latest class of cyathane-xylosides and were isolated from a tropical basidiomycete culture (*Laxitextum incrustatum*) by Süssmuth and co-workers.[322] Laxitextines are closely related to the striatoids, but their A-ring is less oxidized compared to the striatoids' A ring. The laxitextines exhibit anticancer activity in the submicromolar activity range.

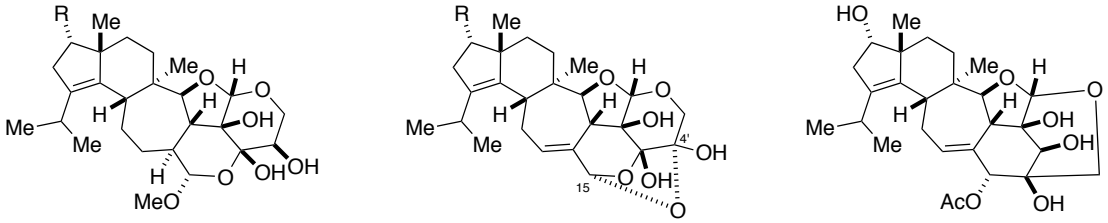


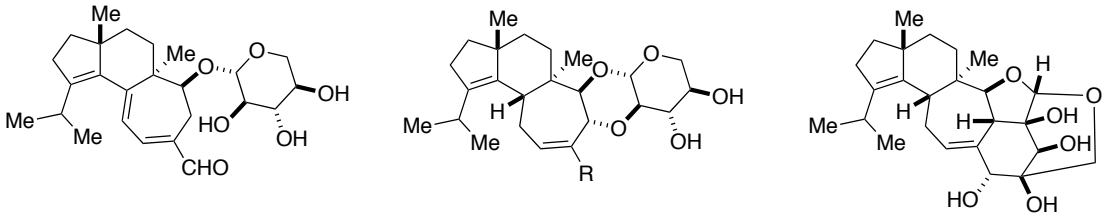
Figure 5.8: Cyathane-xylosides natural products from the laxitextine and striatoid family.

[321] R. Bai, C.-C. Zhang, X. Yin, J. Wie, J.-M. Gao, *J. Nat. Prod*. **2015**, *78*, 783.

[322] C. M. Mudalungu, C. Richter, K. Wittstein, M. A. Abdalla, J. C. Matasyoh, M. Stadler, R. D. Süssmuth, *J. Nat. Prod*. **2016**, *79*, 894.

5.2.5.2 Erinacine and Striatals

Erinacine A (**5.42**), B (**5.43**) and C (**5.44**) were isolated from the fruiting body of *Hericium erinaceum* by Kawagishi and co-workers in 1994.[323] Additional congeners of this family of natural products[324] such as erinacine E[325] (**5.45**) have been isolated from the same biological source (Figure 5.9).[326] Erinacines induce NGF production and might have great potential in the treatment of neurological disorders such as Alzheimer's disease.



erinacine A (**5.42**)

erinacine B (R = CHO, **5.43**)
erinacine C (R = CH_2OH, **5.44**)

erinacine E (**5.45**)

Figure 5.9: Selected erinacine natural products.

Another type of cyathane-xylosides are the striatals, first described by Steglich and co-workers (Figure 5.10).[327] These antibiotics are produced by the basidiomycete species *Cyathus striatus*.[328] However, the striatals (structures **5.46** – **5.49**) themselves have not been isolated, as methanolic extraction leads to hemiacetal formation to give the so-called striatins (structures **5.50** – **5.52**). By treatment with acid, these hemiacetals can be cleaved to give the respective striatals. The striatals show antimicrobial activity against Gram-positive and few Gram-negative bacteria with activities

[323] H. Kawagishi, A. Shimada, R. Shirai, K. Okamoto, F. Ojima, H. Sakamoto, Y. Ishiguro, S. Furukawa, *Tetrahedron Lett*. **1994**, *35*, 1569.

[324] H. Kawagishi, A. Masui, S. Tokuyama, T. Nakamura, *Tetrahedron* **2006**, *62*, 8463.

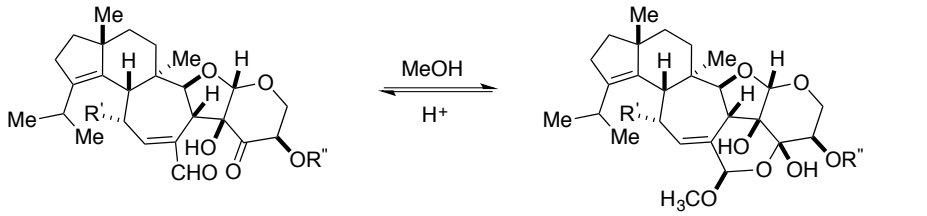
[325] Total synthesis of erinacine E: H. Watanabe, M. Nakada, *J. Am. Chem. Soc*. **2008**, *130*, 1150.

[326] H. Kawagishi, A. Shimada, S. Hosokawa, H. Mori, H. Sakamoto, Y. Ishiguro, S. Sakemi, J. Bordner, N. Kojima, S. Furukawa, *Tetrahedron Lett*. **1996**, *37*, 7399.

[327] a) T. Anke, F. Oberwinkler, W. Steglich, G. Höfle, *J. Antibiot*. **1977**, *30*, 221; b) H. J. Hecht, G. Höfle, W. Steglich, T. Anke, F. Oberwinkler, *J. Chem. Soc. Chem. Comm*. **1978**, 665.

[328] for a review of antiobiotics from higher fungi see: a) W. Steglich, *Pure & Appl. Chem*. **1981** *53*, 1233; b) W. A. Ayer, L. M. Browne, *Tetrahedron* **1981**, *37*, 2199.

in the submicromolar range for *Escherichia coli*, *Pseudomonas fluorescens*, *Staphylococcus aureus*, *Streptomyces viridochromogenes* and *Saccharomyces cerevisiae*.[327a]



striatal A (R' = H, R" = $COCH_3$, **5.46**)
striatal B (R' = OH, R" = $COCH_3$, **5.47**)
striatal C (R' = OH, R" = H, **5.48**)
striatal D (R' = OH, R" = H, **5.49**)

striatin A (R' = H, R" = $COCH_3$, **5.50**)
striatin B (R' = OH, R" = $COCH_3$, **5.51**)
striatin C (R' = OH, R" = H, **5.52**)

Figure 5.10: Striatins are only formed by reaction with methanol during the isolation procedures; upon a treatment with acid the original natural products striatal are recuperated.

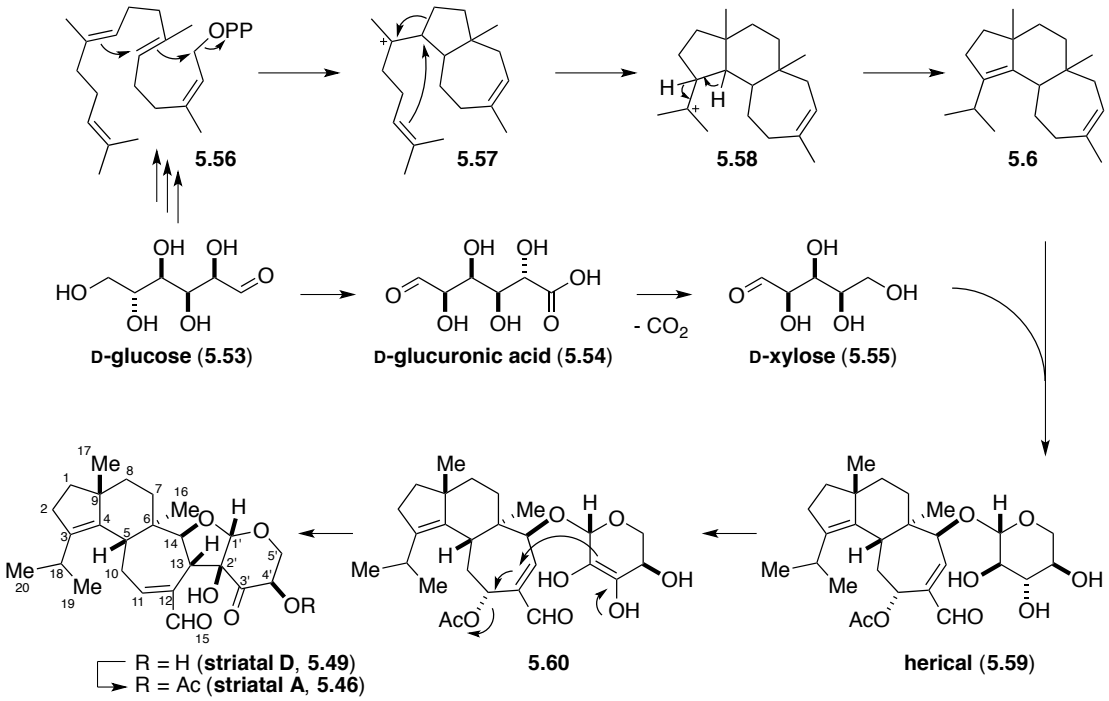
5.3 Cyathane Biosynthesis (Striatal A)

The biosynthesis of the striatals was extensively investigated by feeding the bird's nest fungus *Cyathus striatus* with isotope-labeled glucose ([1-^{13}C] or [2-^{13}C]).[329] These studies showed that the labeled glucose (**5.53**) acts as a precursor in two ways (Scheme 5.1). First, it is incorporated into the terpene structure *via* the mevalonate pathway[330] and secondly, the glucose (**5.53**) is converted into the xylose moiety. D-Glucose (**5.53**) is first oxidized to D-glucoronic acid (**5.54**) and afterwards D-xylose (**5.55**) is formed by decarboxylation. The terpene building block is also obtained from D-glucose (**5.53**), which is converted to geranyl pyrophosphate (**5.56**) in the mevalonate pathway. Geranylgeranyl pyrophosphate (**5.56**) then serves as a building block for the 5-7-membered ring system (**5.57**). The trisubstituted olefin attacks the carbon center adjacent to the tertiary carbocation and induces a 1,2-alkyl migration (Wagner-Meerwein shift) so that the 5-6-7-ring system (**5.58**) is formed. Subsequent hydride shift and deprotonation lead to the core structure **5.6** of the cyathanes. At this stage, combination with the pentose **5.55** unit gives access to herical (**5.59**), which had also been identified from

[329] T. Anke, U. Rabe, P. Schu, T. Eizenhöfer, M. Schrage, W. Steglich, *Z. Naturforsch*. **2002**, *57,* 263.

[330] J. L. Goldstein, M. S. Brown, *Nature* **1990**, *343*, 425.

the fungal culture. Further oxidation leads to an enol **5.60** on the pentose moiety, which attacks the cyathane scaffold in a S_N2' fashion to form striatal D (**5.49**). Acetylation of the free hydroxy group in the pentose unit yields striatal A (**5.46**).



Scheme 5.1: Biosynthesis of striatal A (**5.46**).

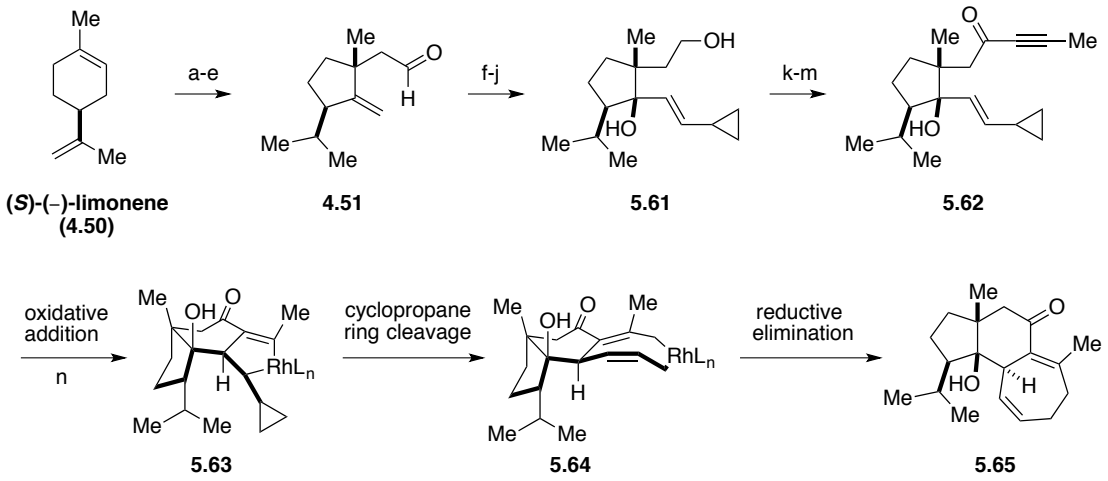
5.4 Syntheses of Cyathan Natural Products

5.4.1 Wender's Rhodium-Catalyzed [5 + 2] Cycloaddition Approach

Wender's strategy features a rhodium-catalyzed cycloaddition as key step to set up the cyathane core structure (Scheme 5.2).[277] Starting from commercially available (*S*)-limonene (**4.50**), the first quaternary carbon center was introduced *via* a Claisen-rearrangement with a diastereomeric ratio of 10:1 in favor of the desired aldehyde **4.51**. A Lemieux-Johnson oxidation of the terminal olefin and a Ce(III)-mediated 1,2-addition of lithium cyclopropylacetylide on the keton followed reduction of the alkyne with $LiAlH_4$/NaOMe furnished olefin **5.61**.[331] Oxidation of the alcohol to the aldehyde and 1,2-addition of 1-propynylmagnesium bromide followed by oxidation of the secondary alcohol to the ketone furnished enyne-vinylcyclopropane precursor **5.62**. The rhodium complex is supposed to induce ring closure by oxidative addition to the alkyne and the alkene to give intermediate **5.63**. Strain-induced cyclopropane cleavage furnishes a metallacyclooctadiene intermediate **5.64**, which yields the tricyclic core structure **5.65** upon reductive elimination. The regioselectivity of this sequence has been studied by the Wender group in prior work on 1,1-disubstituted cyclopropanes.[332] However, the enantioselectivity of this transformation might be better due to pre-coordination of the tertiary alcohol to the metal center, which then directs the attack of the Rh-complex on the substrate.

[331] E. J. Corey, J. A. Katzenellenbogen, G. A. Posner, *J. Am. Chem. Soc.* **1967**, *89*, 4245.

[332] P. A. Wender, A. J. Dyckman, C. O. Husfeld, D. Kadereit, J. A. Love, H. Rieck, *J. Am. Chem. Soc.* **1999**, *121*, 10442.



Scheme 5.2: Wender's approach towards the tricyclic core structure **5.65** using a rhodium catalyzed [5 + 2] cycloaddition. a) H_2, PtO_2, 94%; b) OsO_4, $NaIO_4$, THF/H_2O, 97%; c) piperidine, AcOH, benzene, reflux, 75%; d) DIBAL-H, Et_2O, 0 °C, 96%; e) $EtOCH{=}CH_2$, $Hg(OAc)_2$, reflux, then toluene, reflux, 90%; f) $NaBH_4$, MeOH/H_2O, 95%; g) TBSCl, imidazole, DMF, 90%; h) O_3, CH_2Cl_2, –78 °C, Me_2S, 65%; i) 1-ethynylcyclopropane, *n*-BuLi, $CeCl_3$, 0 °C, 91%; j) $LiAlH_4$, NaOMe, THF, reflux, 69%; k) DMP, $NaHCO_3$, CH_2Cl_2; l) MeCCMgBr, THF, 75% (over two steps); m) DMP, $NaHCO_3$, CH_2Cl_2, 93%; n) $[Rh(CO)_2Cl]_2$, 1,2-dichloroethane, 80 °C, 3.5 h, 90%; L = ligand, n = number of ligands.

5.4.2 Nakada's Synthesis of (–)-Scabronine G

The group of Nakada reported a 19 step synthesis (21% yield) of (–)-scabronine G (**5.66**, Scheme 5.3).[333] Its synthesis features an impressive oxidative dearomatization and an intramolecular Diels-Alder reaction with inverse-electron-demand (IEDDA). Starting from the aromatic aldehyde[334] **5.67**, a propargylation followed by deoxygenation of the secondary alcohol and subsequent lithiation of the terminal alkyne give a nucleophile that cleanly adds to the Weinreb amide **5.68**[335] to yield the desired ketone **5.69**. The allene **5.70** was obtained by reduction of the ketone and phosphorylation of the resulting secondary alcohol followed by addition of isopropylmagnesium chloride in the presence of copper(I) cyanide. The TIPS group was removed

[333] Y. Kobayakawa, M. Nakada, *Angew. Chem. Int. Ed.* **2013**, *52*, 7569.

[334] T. S. Kaufman, *J. Chem. Soc. Perkin Trans. 1* **1996**, 2497.

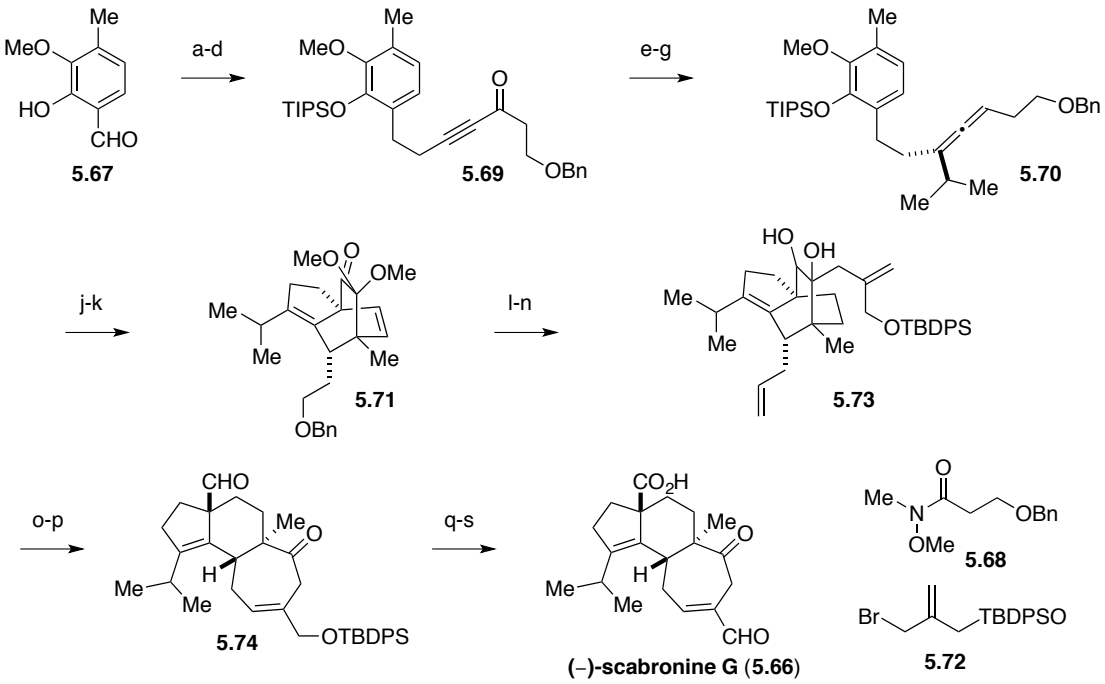
[335] K. C. Nicolaou, K. P. Cole, M. O. Frederick, R. J. Aversa, R. M. Denton, *Angew. Chem. Int. Ed*. **2007**, *46*, 8875.

and the resulting free alcohol was oxidized in the presence of PIDA to form the *o*-benzoquinone mono-dimethylacetal intermediate, which spontaneously undergoes an IEDDA reaction to the desired cyclic product **5.71** in 97% yield and with an excellent enantiomeric ratio of 95%. The authors claim that steric repulsion between the dimethyl acetal and the 2-benzyloxyethyl group in the Diels-Alder reaction's transition state favors formation of the desired product **5.71**. Removal of the benzylic protecting group, Swern oxidation of the primary alcohol and a Wittig reaction furnish the terminal alkene. The ketone was reduced to the secondary alcohol and the acetal was hydrolyzed to yield the α-hydroxy ketone intermediate, which was subsequently treated with an allylzinc reagent **5.72**[336] to furnish the *cis*-1,2-diol **5.73**. Oxidative cleavage of the diol in the presence of PIDA[337] yielded a ketoaldehyde, which was subjected to a metathesis reaction with Grubbs II catalyst to yield the seven-membered ring **5.74**. Finally, the silyl-protecting group was removed and a Pinnick oxidation followed by Dess-Martin oxidation furnished the natural product (−)-scabronine G (**5.66**). Biological testing revealed that the methyl ester derivative of scabronine is a more potent stimulator of neurite outgrowth than the natural product itself.[311b,338]

[336] R. W. Heidebrecht, Jr., B. Gulledge, S. F. Martin, *Org. Lett*. **2010**, *12*, 2492.

[337] K. C. Nicolaou, V. A. Adsool, C. R. H. Hale, *Org. Lett*. **2010**, *12*, 1552.

[338] Y. Obara, H. Kobayashi, T. Ohta, Y. Ohizumi, N. Nakahata, *Mol. Pharmacol.* **2001**, *59*, 1287.



Scheme 5.3: Nakada's synthesis of (–)-scabronine G (**5.66**). a) TIPSCl, imidazole, DMF, 40 °C, 83%; b) propargyl bromide, Zn, $TiCl_4$, THF, 0 °C; c) Et_3SiH, BF_3 x OEt_2, CH_2Cl_2, 0 °C, 84% (over two steps); d) *n*-BuLi, **5.68**, THF, –78 °C to r.t., 89 %; e) Ru[(*R*,*R*)-Tsdpen](*p*-cymene), ^{i}PrOH, r.t., 92% (95% *ee*); f) $(EtO)_2P(O)Cl$, DMAP, Et_3N, CH_2Cl_2, r.t., 97%; g) ^{i}PrMgCl, CuCN x 2 LiCl, THF, –78 °C, quant.; h) TBAF, THF, 0 °C, 97 % (95 % *ee*); i) PIDA, MeOH, r.t., 7 d, 97%; j) H_2, Pd/C, EtOAc, r.t., 92%, (95% *ee*, >99% *ee* (after recryst.)); k) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C to 0 °C, 98%; l) Ph_3PCH_3Br, *t*-BuOK, THF, 0 °C, 99%; m) $NaBH_4$, MeOH, 0 °C; then, 3 N HCl (aq.), 95%; n) **5.72**, Zn, THF, r.t., 91 %; o) PIDA, CH_2Cl_2, r.t., 90%; p) Grubbs II cat., CH_2Cl_2, reflux, 98%; q) TBAF, AcOH, THF, r.t., 70%; r) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF, *t*-BuOH, H_2O, r.t., 97 %; s) DMP, CH_2Cl_2, 0 °C, 89%.

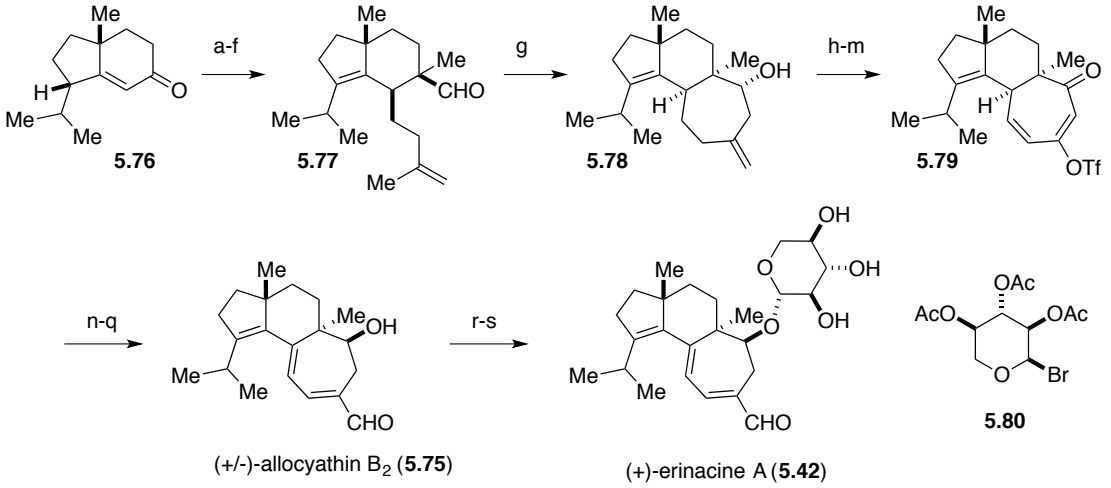
5.4.3 Snider's Synthesis of (±)-Allocyathin B_2 and (+)-Erinacine A

Snider and co-workers reported the preparation of two natural products by the same synthetic route.[339] (±)-Allocyathin B_2[340] (**5.75**) was obtained in 19 steps (>5% yield) and erinacine A (**5.42**) by two additional steps from **5.75** (Scheme 5.4). The seven-membered ring was constructed by an intramolecular ene-reaction. Starting from the advanced enone intermediate

[339] B. B. Snider, N. H. Vo, S. V. O'Neil, *J. Org. Chem*. **1998**, *63*, 4732.

[340] Another total synthesis was achieved by Tori and co-workers: a) M. Tori, N. Toyoda, M. Sono, *J. Org. Chem*. **1998**, *63*, 306; for an enantioselective approach see: b) B. M. Trost, L. Dong and G. M. Schroeder, *J. Am. Chem. Soc*. **2005**, *127*, 2844; c) B. M. Trost, L. Dong, G. M. Schroeder, *J. Am. Chem. Soc*. **2005**, *127*, 10259.

5.76,[341] a deprotonation in δ-position and reaction with Tf_2O furnished the corresponding vinyltriflate. A Pd(II) mediated carbonylation yielded the methyl ester, which was directly reduced to the alcohol and subsequently oxidized to the aldehyde by MnO_2. Thereafter, reaction with the cuprate gave the axial addition product. α-Methylation afforded a mixture of methylated diastereomers **5.77** in a ratio of 15:1 (major isomer shown in Scheme 5.4). An $AlMe_2Cl$-mediated ene-reaction gave access to the seven-membered ring system **5.78** as a single diastereomer. Protection of the alcohol, oxidative cleavage of the terminal olefin, enone formation with PhSeCl and H_2O_2, followed by silyl deprotection, oxidation of the alcohol and triflation of the enol furnished the desired vinyltriflate **5.79**. The methyl ester was installed by a Pd-mediated carbonylation, followed by double bond isomerization under alkaline conditions. A global reduction of both the ketone and the ester furnished the diol, whose primary alcohol group was chemoselectively oxidized to the aldehyde in the natural product (±)-allocyathin B_2 (**5.75**). Finally, glycosylation with triacetyl-α-D-xyloyrhamnosyl bromide (**5.80**) gave an inseparable mixture of the two anomers in a 1:1 ratio. Deprotection of the acetyl residues yielded the natural product erinacine A (**5.42**), known as a NGF stimulator.[342]



Scheme 5.4: Total Synthesis of (±)-allocyathin B_2 (**5.75**) and (+)-erinacine A (**5.42**) by Snider and co-workers. a) proton sponge, Tf_2O, 88%; b) $Pd(OAc)_2$, Ph_3P, CO, $^iPr_2NEt$, MeOH, 85%; c) DIBAL-H, 97%; d) MnO_2, 95%; e) $H_2C{=}C(CH_3)CH_2CH_2MgBr$, CuBr x DMS, TMSCl, HMPA, 91%; f) *t*-BuOK, MeI, 70%; g) Me_2AlCl, 87%; h) $^iPrMe_2SiCl$, imid., 95%; i) OsO_4, KIO_4, 77%; j)

[341] B. B. Snider, D. J. Rodini, J. van Straten, *J. Am. Chem. Soc.* **1980**, *102*, 5872.

[342] M. Shimbo, H. Kawagishi, H. Yokogoshi, *Nutrition Research* **2005**, *25*, 617.

LiHMDS, PhSeCl, H_2O_2, 72%; k) HOAc, H_2O, THF; l) DMP, 72% (over two steps); m) KHMDS, $PhNTf_2$, 75%; n) $Pd(OAc)_2$, Ph_3P, CO, $^iPr_2NEt$, MeOH, 75%; o) Et_3N, MeOH, 94%; p) LAH, 89%; q) MnO_2, 94%; r) **5.80**, $Hg(CN)_2$, $HgCl_2$, 34%; s) K_2CO_3, >90%.

5.4.4 Nakada's Enantioselective Total Synthesis of (–)-Erinacine B

The group of Nakada reported on an enantioselective total synthesis of (–)-erinacine B (**5.43**) featuring a C1-ring expansion (Scheme 5.5).[343] The synthesis starts from the tricyclic intermediate **5.81**, which has already been described in the synthesis of (+)-allocyathin B_2 (**5.75**).[344] Elimination of water upon reaction of the alcohol with thionyl chloride, removal of the MPM protecting group and 1,4-reduction of the enone mediated by SmI_2 yielded ketone **5.82**. The isopropyl group was introduced by reaction with an isopropenyl cerium reagent and subsequent hydrogenation of the terminal olefin. The secondary alcohol was oxidized with DMP and the tertiary alcohol was subjected to an E1 elimination and the obtained trisubstituted olefin was isomerized under acidic conditions to form the thermodynamically more stable tetrasubstituted olefin **5.83**. Applying Hagesawa's conditions,[345] ring expansion was achieved by preparing the β-keto ester by reaction of the ketone with Mander's reagent,[346] iodomethylation with diiodomethane and SmI_2-mediated rearrangement to give the seven-membered γ-keto ester **5.84**. The corresponding TMS-enol ether was treated with PhSeCl and H_2O_2 to furnish the alkene in a selenoxide elimination. Base-induced isomerization and reduction of both ketone and ester furnished the desired 1,4-diol **5.85**. A vanadyl acetylacetonate-mediated oxidation installed the desired epoxide as a single diastereomer. The primary alcohol was selectively protected, and the secondary alcohol oxidized to the ketone **5.86** by DMP. The epoxide was regioselectively opened and the resulting secondary alcohol protected to furnish enone **5.87**. A CBS-reduction afforded the desired alcohol **5.88**. The glycosylation proved to be challenging, as no conversion was observed with

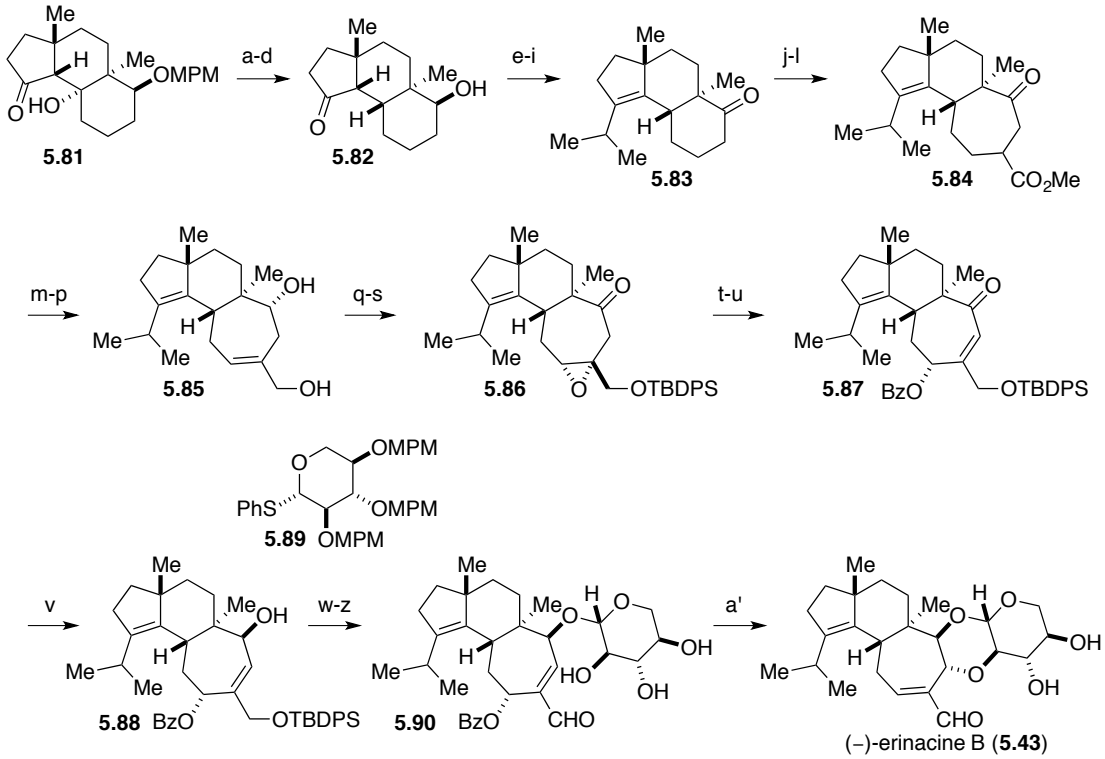
[343] H. Watanabe, M. Takano, A. Umino, T. Ito, H. Ishikawa, M. Nakada, *Org. Lett*. **2007**, *9*, 359.

[344] M. Takano, A. Umino, M. Nakada, *Org. Lett.* **2004**, *6*, 4897.

[345] E. Hasegawa, T. Kitazume, K. Suzuki, E. Tosaka, *Tetrahedron Lett.* **1998**, *39*, 4059.

[346] L. N. Mander, S. P. Sethi, *Tetrahedron Lett.* **1983**, *24*, 5425.

various standard glycosylation protocols. Finally, MeOTf-mediated coupling with an MPM-protected derivative **5.89** of xylose phenyl thiol ether as glycosyl donor furnished the desired glycoside linkage with an anomeric ratio of 1:3.5 (α:β). The silyl protecting group was removed and the allylic alcohol oxidized by DMP. Cleavage of the MPM protecting groups gave sugar **5.90**, which up treatment with base brought about the ring closing S_N2' reaction with loss of benzoate to yield (–)-erinacine B (**5.43**) as a single diastereomer. (–)-Erinacine B (**5.43**) is a highly potent stimulator of NGF, even stronger as the control epinephrine.[323]



Scheme 5.5: Nakada's enantioselective synthesis of (–)-erinacine B (**5.43**). a) $SOCl_2$, py, CH_2Cl_2, 0 °C to r.t., 91%; b) DBU, benzene, reflux, 92%; c) DDQ, CH_2Cl_2, *t*-BuOH, H_2O, 0 °C to r.t., quant.; d) SmI_2, HMPA, THF, –15 °C to r.t., 94%; e) 2-bromopropene, *t*-BuLi, $CeCl_3$, Et_2O, THF, –78 °C, 84%; f) H_2, Pd/C, MeOH, r.t., 95%; g) DMP, CH_2Cl_2, r.t., 91%; h) $SOCl_2$, py, CH_2Cl_2, 0 °C to r.t., quant.; i) TsOH, benzene, reflux, quant.; j) LiHMDS, $NCCO_2Me$, THF, –78 °C, 79%; k) CH_2I_2, TBAF, THF, 0 °C to r.t., 66%; l) SmI_2, HMPA, THF, –78 °C, 81%; m) TMSOTf, Et_3N, CH_2Cl_2, 0 °C; n) PhSeCl, THF, –78 °C, then H_2O_2, py, 0 °C to r.t., 91% (over two steps); o) DBU, benzene, reflux, 98%; p) DIBAL-H, CH_2Cl_2, –78 °C, 96% (d.r. = 10:1); q) TBHP, $VO(acac)_2$, CH_2Cl_2, –40 °C; r) TBDPSCl, imid., DMF, r.t.; s) DMP, CH_2Cl_2, r.t., 80% (over three steps); t) DBU, C_6H_6, 50 °C; u) Bz_2O, py, DMAP, $(CH_2Cl)_2$, 50 °C, 78% (over two steps); v) (*R*)-CBS, BH_3-SMe_2, CH_2Cl_2, –40 °C, 95%; w) **5.89**, MeOTf, Et_2O, r.t.; x) HF x py,

THF, 0 °C to r.t., 77% (over two steps, (α/β = 1:3.5); y) DMP, CH_2Cl_2, r.t., 96%; z) TFA, CH_2Cl_2, –20 °C, quant.; a') Et_3N, LiBr, THF, r.t., 74% (over three steps).

5.4.5 Gademann's Synthesis of Cyrneine A

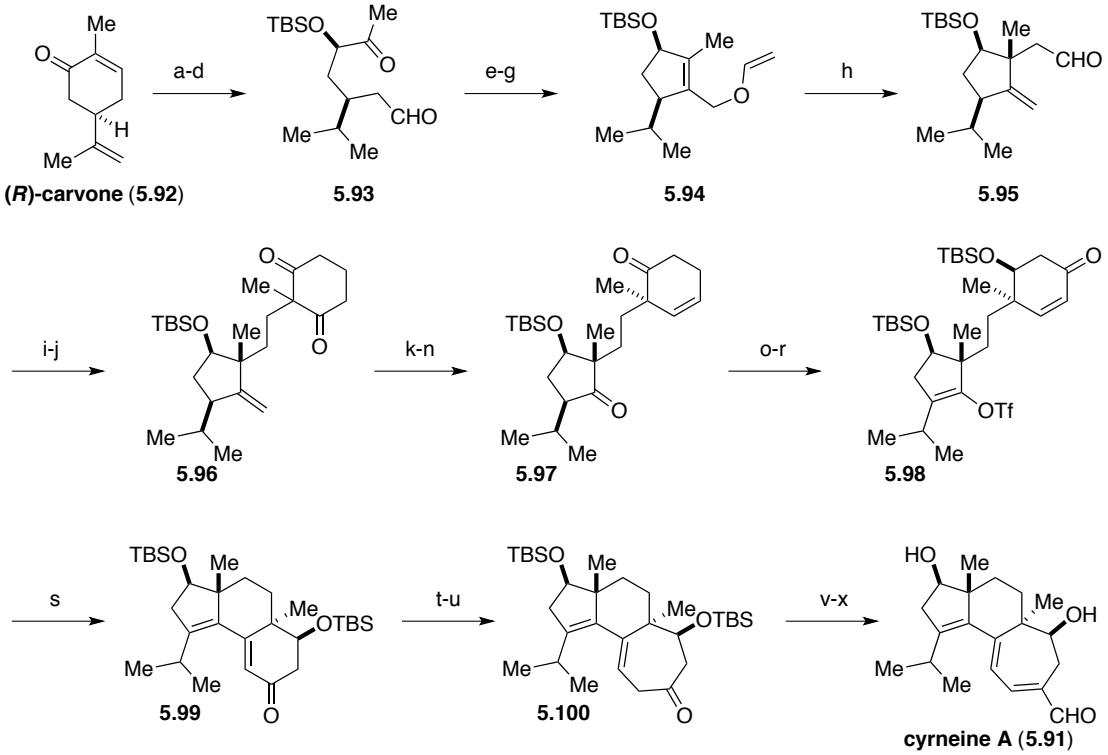
In 2012, Gademann and co-workers reported on the first successful total synthesis of a natural product from the cyrneine family (Scheme 5.6). Their route to cyrneine A[319] (**5.91**) contains 24 linear steps[347] and features a Heck-cyclization to form the B-ring and a Yamamoto ring expansion.[348] Starting from enantiopure (*R*)-carvone (**5.92**), the ketone was reduced, the resulting alcohol protected by TBS and the exocyclic double bond hydrogenated. Ozonolysis with reductive workup led to the 1,6-ketoaldehyde **5.93**. An intramoelcular aldol condensation mediated by piperidinium acetate gave the desired cyclopentene ring and the aldehyde was reduced to the alcohol and submitted to a Hg(II)-mediated transetherification to obtain allylether **5.94**. The quaternary carbon center was installed by Claisen rearrangement to furnish the aldehyde **5.95**. An organocatalytic Knoevenagel condensation with cyclohexa-1,3-dione and subsequent double bond reduction with Hantzsch ester yielded the unstable diketone, which was directly methylated to furnish 1,3-diketone **5.96**. Ozonolysis of the exocyclic olefin and position- and diastereoselective Luche reduction yielded an alcohol intermediate, which was subjected to mesylation and elimination to furnish the desired cyclohex-3-en-1-one derivative **5.97**. The latter was reduced by sodium borohydride and the resulting alcohol protected with TBS. Formation of the enol triflate and subsequent allylic oxidation with CrO_3 gave the enone **5.98**, which set the stage of the intramolecular Heck-cyclization that furnished tricycle **5.99**. α-Addition of lithium dibromomethanide and subsequent treatment with *n*-BuLi yielded the cyclohept-3-en-1-one derivative **5.100** in a Yamamoto ring expansion reaction. Formation of the vinyl triflate was followed by Pd-catalyzed reductive carbonylation[349] to give the desired aldehyde. After global

[347] E. Elamparuthi, C. Fellay, M. Neuburger, K. Gademann, *Angew. Chem. Int. Ed*. **2012**, *51*, 4071.

[348] H. Taguchi, H. Yamamoto, H. Nozaki, *Bull. Chem. Soc. Jpn*. **1977**, *50*, 1592; b) H. Taguchi, H. Yamamoto, H. Nozaki, *J. Am. Chem. Soc*. **1974**, *96*, 6510.

[349] P. V. Baillargeon, K. J. Stille, *J. Am. Chem. Soc*. **1986**, *108*, 452.

deprotection, cyrneine A (**5.91**) was obtained and its structure confirmed by single crystal X-ray structure analysis. Cyrneine A (**5.91**) promotes neurite outgrowth in the absence of NGF with an activity comparable to NGF.[319]



Scheme 5.6: Gademann's enantioselective total synthesis of cyrneine A (**5.91**). a) $LiAlH_4$, Et_2O, −78 °C, 15 min; b) TBSCl, imidazole, CH_2Cl_2, r.t., 1.5 h; c) PtO_2/H_2, THF, r.t., 4 h, 96% (over three steps); d) O_3, Zn/AcOH, CH_2Cl_2/MeOH (5:1), −78 °C, r.t., 1 h, 89%; e) piperidine, AcOH, Et_2O, 70 °C, 20 h, 92%; f) $NaBH_4$, MeOH, 0 °C, 15 min, 88%; g) $Hg(OAc)_2$, ethyl vinyl ether, 60 °C, 24 h, 94%; h) toluene, 175 °C, 16 h, 81%, d.r. = 10:1; i) L-proline, cyclohexa-1,3-diene, Hantzsch ester, CH_2Cl_2, 3 h, r.t.; j) MeI, DBU, LiI, THF, 14 h, 75 °C, 73% (over two steps); k) O_3, CH_2Cl_2, SMe_2, −78 °C, 1 h, 83%; l) $CeCl_3$ x 7 H_2O, $NaBH_4$, THF/MeOH (1:5), −78 °C, 20 min, 68%; m) $(MeSO_2)_2O$, pyridine, DMAP, 5 h, r.t., 88%; n) LiBr, Li_2CO_3, DMF, 140 °C, 1 h, 79%; o) $NaBH_4$, MeOH, 0 °C, 20 min, 86%; p) TBSOTf, 2,6-lutidine, CH_2Cl_2, 2 h, r.t., 85%; q) KHMDS, $PhNTf_2$, THF, −78 °C, 3 h, 83%; r) CrO_3, DMP, CH_2Cl_2, 18 h, r.t., 71%; s) $Pd(OAc)_2$, TBABr, PPh_3, K_2CO_3, toluene, 120 °C, 1 h, 63%; t) CH_2Br_2, LiTMP, THF, −78 °C, 20 min, 76%; u) *n*-BuLi, THF, −90 °C, 30 min, 68%; v) KHMDS, $PhNTf_2$, THF, −78 °C, 20 min, 81%; w) $Pd(PPh_3)_4$, LiCl, CO, *n*-Bu_3SnH, THF, 80 °C, 3 h, 77%; x) TBAF, THF, r.t., 14 h, 84%.

5.5 Goal of this Study, Retrosynthetic Analysis and Synthetic Approaches towards the Tricyclic ABC Core Structure of Striatal

The tricyclic core structure of striatal A (**5.46**) is similar to the neurotrophic active natural product cyrneine A (**5.91**),[347] which was recently synthesized in our group. The structural differences are the missing hydroxy function at C-1 and double bond between C-5 and C-10 as shown in Figure 5.11. By adapting the synthetic precursor (*R*)-carvone (**5.92**) to (*S*)-limonene (**4.50**), the cyathane core structure should be in general accessible following the established synthetic route. Furthermore the planned route can be shorten by a few steps (lacking of initial ketone and hydroxy manipulation) towards the cyathane core structure of striatal A (**5.46**). To our best knowledge, the striatals had not yet been synthesized and a general route towards this highly complex and interesting natural products should be established.

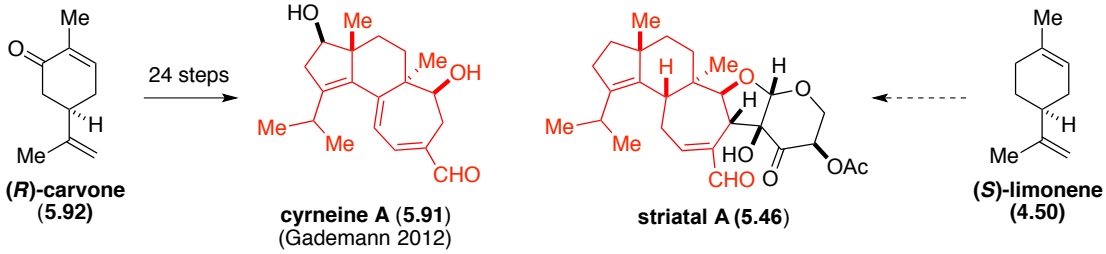
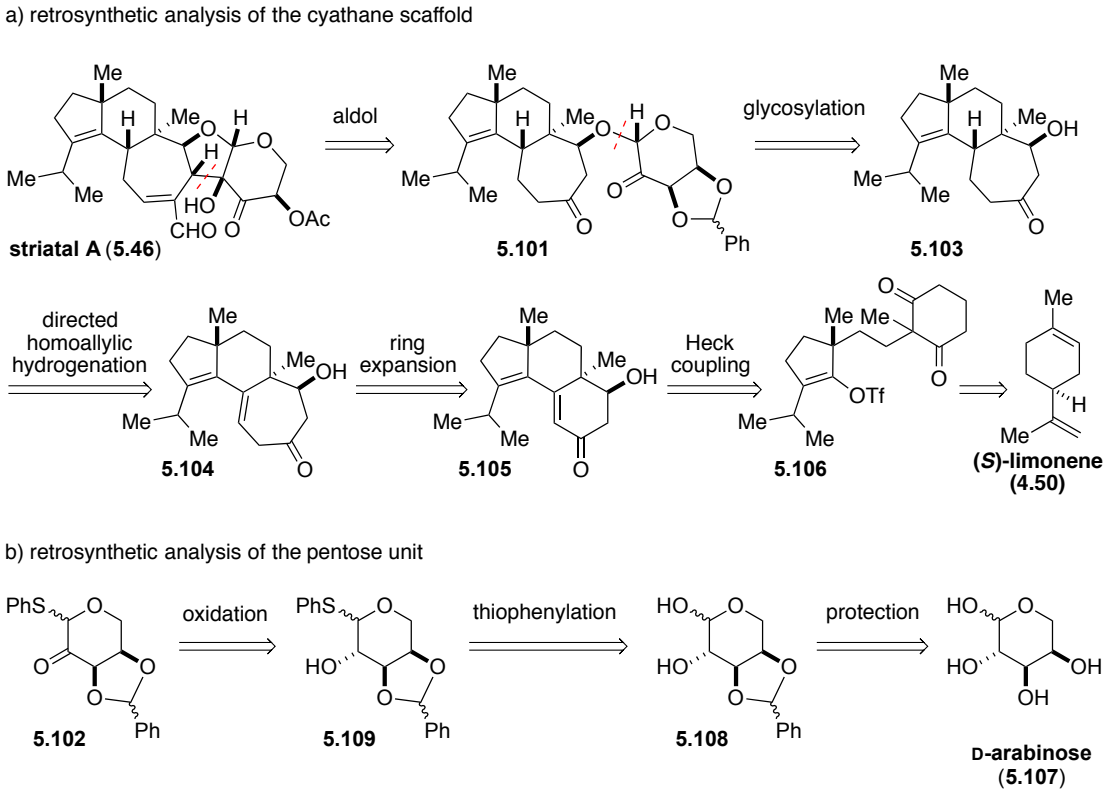


Figure 5.11: Structural similarity (shown in red) of cyrneine A (**5.91**) and striatal A (**5.46**).

The retrosynthethic parts of the cyathane and the pentose unit are illustrated in Scheme 5.7a, respectively 5.7b. According to the biomimetic approach of Nakada,[325] our approach is facing the opposite way *via* a nucleophilic attack of the cyathane to the pentose unit. Therefore, the C-13-C-2'-bond can be connected *via* an aldol reaction out of intermediate **5.101**. Nakada was already successful in the installation of the pentose unit *via* a glycosylation,[325] thus using a modified pentose unit **5.102** with the cyathane structure **5.103** should be feasible. The hydroxy group should support a homoallylic hydrogenation of the trisubstituted olefin **5.104**. Furthermore, a shielding effect of the adjacent methyl group at C-16 might favor a concave

hydrogenation. The ring expansion out of the 5-6-6-membered ring system **5.105** follows our established route, as well as the Heck cyclization from vinyltriflate **5.106**.[347] The lacking oxygen function at position C-1 yields in an adopted starting material, thus our synthesis would start from commercially available (*S*)-limonene (**4.50**).

The pentose unit itself is derived from D-arabinose (**5.107**). First the *syn*-diol is protected[350] **5.108** and the anomeric hydroxy function is replaced by a thiophenol moiety[351] to furnish thiophenol **5.109**. Last the unprotected hydroxy function is oxidized to the ketone yielding the pentose building block **5.102**.[352]



Scheme 5.7: Retrosynthetic analysis of striatal A (**5.46**) and the pentose unit **5.102**.

[350] N. K. Jalsa, *Tetrahedron Lett*. **2011**, *52*, 6587.

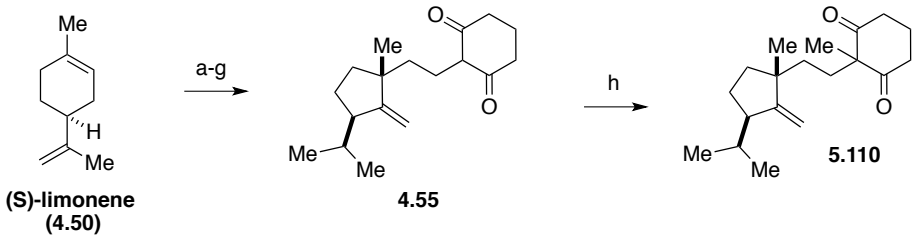
[351] A. Fürstner, *Liebigs Annalen der Chemie* **1993**, *11*, 1211.

[352] H.-L. Chuang, R- C. Sawant, S.-Y. Luo, *Synlett* **2013**, *24*, 0522.

5.5.1 Synthetic Studies on Striatal A

5.5.1.1 Cyrneine A Approach

The synthesis was conducted with enantiopure (*S*)-limonene (**4.50**) as the starting material (Scheme 5.8). We first followed the footsteps of Wender,[277] but optimized conditions were finally applied. The first steps from (*S*)-limonene (**4.50**) to diketone **4.55** are in detailed discussed in the endoperoxide chapter of this thesis (see chapter four).[195] The instable key building block **4.55** was directly methylated to the methyldiketone **5.110** in a low yield of 34%. The low yield arises from a competing *O*-alkylation event. Furthermore, the instable precursor forms spontaneous endoperoxides in the presence of oxygen.[195]

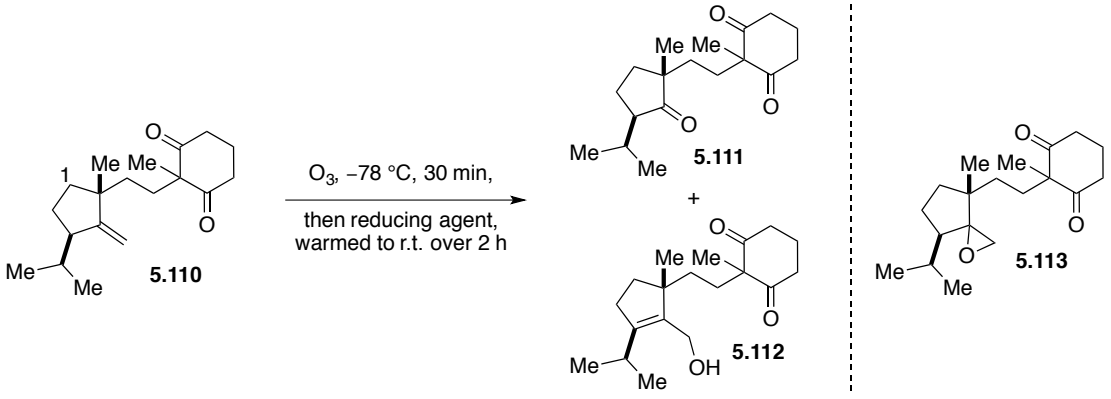


(S)-limonene (4.50) **4.55**

Scheme 5.8: Synthesis of the methylated intermediate **5.110**. a) H_2, PtO_2 (cat.), THF, r.t., 94%; b) O_3, Zn/AcOH, CH_2Cl_2/MeOH (5:1), –78 °C, 94%; c) piperidine, AcOH, benzene, 110 °C, 75%; d) DIBAL-H, Et_2O, 0 °C, 96%; e) 1,1-dimethoxyethyl(dimethyl)amine, *p*-xylene, 16 h, 150 °C, 95% (d.r. = 24:1); f) 1,1,3,3-tetramethyldisiloxane, $Ti(O^iPr)_4$, THF, r.t., 18 h, 95%; g) L-proline, Hanztsch ester, CH_2Cl_2, r.t., 19 h, 91%; h) MeI, DBU, LiI, THF, 80 °C, 15 h, 34%.

The installation of the ketone function **5.111** was surprisingly quite challenging and summarized in Table 5.1. Applying our reported ozonolysis condition[347] on the olefin **5.110** yielded a complex mixture (Table 5.1, entry 1). Therefore we searched for more appropriate neutral reducing agents. The crude mixture using DMS (entry 2 – 4) as reducing agents showed the formation of several products, which are a ketone **5.111,** allylic alcohol **5.112** and epoxide **5.113**. The isolation yielded the ketone **5.111** and the allylic alcohol **5.112** in minor amounts. The epoxide **5.113** was observed by ^{1}H-NMR analysis, but could not be isolated and might have opened to the allylic alcohol upon SiO_2-flash column chromatography purification. Furthermore, sterical hindered olefins are known to form epoxides under ozonolysis

conditions.[353] The solvent was swapped to MeOH and an improved yield of 40% for the ketone **5.111** was obtained (entry 5). Nevertheless, the allylic alcohol **5.112** as a competing side reaction was observed too. Quenching the reaction with PPh_3 gave 26% yield of the ketone **5.111** in (entry 6). Additionally a novel method was tested, which uses instead of a reducing agent only pyridine in a catalytic amount. However, only the alcohol **5.112** product and an unidentified by-product was observed (entry 7). Compared to the reported method,[347] only the OTBS-function at position C-1 is missing, but this seems to have a tremendous impact on the accessibility of the terminal olefin. The 5-membered ring junction probably leads to a sterically demanding olefin.[353] Furthermore, the methyldiketone moiety might have a shielding effect, which makes an attack for the reagents not suitable.



entry	reducing agent	solvent	observation
1[347]	Zn (4 eq) AcOH (4 eq)	CH_2Cl_2/MeOH (5:1)	complex mixture
2	DMS (2 eq)	CH_2Cl_2	16% **5.111,** n.d. **5.112**
3[354]	DMS (2 eq)	CH_2Cl_2	25% **5.111,** n.d. **5.112**
4	DMS (2 eq)	CH_2Cl_2	35% **5.111**, 25% **5.112**
5	DMS (2 eq)	MeOH	40% **5.111,** n.d. **5.112**
6	PPh_3 (2 eq)	CH_2Cl_2	26% **5.111**

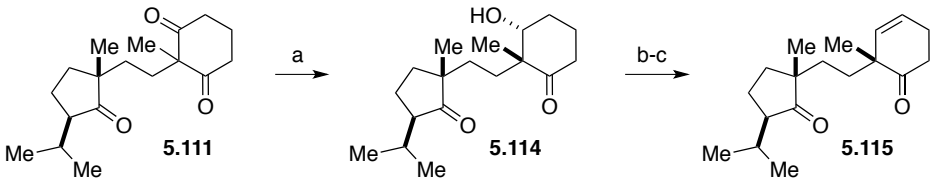
[353] P. S. Bailey, H. H. Hwang, C.-Y. Chiang, *J. Org. Chem*. **1985**, *50*, 231.

[354] Scale was increased by a factor of 5.

7[355]	py (cat.)	CH_2Cl_2	**5.112** formed

Table 5.1: Optimization for the oxidative cleavage of the terminal olefin.

The synthesis was continued by applying Luche's condition on the ketone **5.111** yielding the desired alcohol **5.114** in 67% and a low diastereomeric ratio of 1.7:1 (Scheme 5.9). After separation of the diastereomers, the hydroxy group was mesylated and after a short work-up directly eliminated to the olefin **5.115**. Both steps yielded in several unknown side-products. Based on the low yields and general sluggish outcome of the reactions, we thought about using more convenient diketone modifications. Initial studies on diketone modifications were already conducted by Simon Glauser (University of Basel) on similar molecules.[356]



Scheme 5.9: Applying the reported diketone modification sequence. a) $CeCl_3$ x 7 H_2O, $NaBH_4$, MeOH, THF, –78 °C, 1 h, 67%, d.r. = 1:1.7; b) $(MeSO_2)O$, DMAP, r.t., 22 h, n.d.; c) LiBr, Li_2CO_3, DMF, 140 °C, 1 h, n.d.

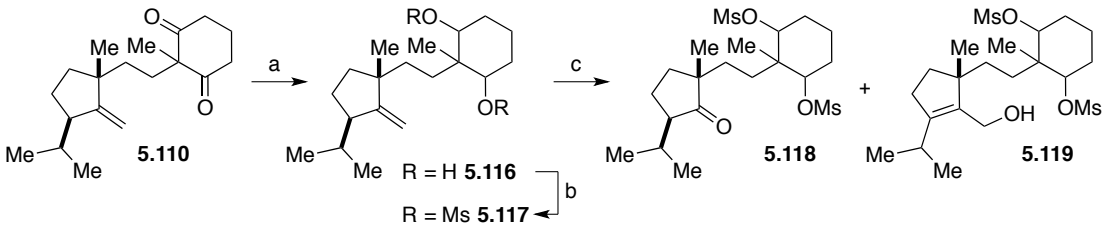
The diketone **5.110** was first treated with various reducing agents (Scheme 5.10). $NaBH_4$ showed a complex mixture (50% of diol **5.116**) and $LiBEt_3H$[357] only decomposition of the starting material **5.110**. Finally, lithium tri-*tert*-butoxyaluminium hydride (LTBA) was superior and yielded the desired diol **5.116** in good yields and as a single diastereomer.[358] The chiral center identification was not further investigated, due to a planned elimination step later in this sequence. The diol **5.116** was mesylated to obtain the bis-mesylate **5.117.** We applied again the ozonolysis conditions and the desired ketone **5.118** was formed in 30% along with the allylic alcohol **5.119**.

[355] R. Willand-Charnley, T. J. Fisher, B. M. Johnson, P. H. Dussault, *Org. Lett*. **2012**, *14*, 2242.

[356] Simon Glauser, Master Thesis in Chemistry, University of Basel **2012**.

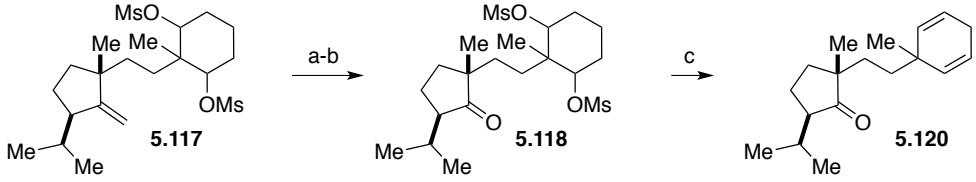
[357] A. Krief, D. Surleraux, N. Ropson, *Tetrahedron: Asymmetry* **1993**, *4*, 289.

[358] K. C. Nicolaou, J. A. Pfefferkorn, S. Kim. H. X. Wie, *J. Am. Chem. Soc*. **1999**, *121*, 4724.



Scheme 5.10: Improved diketone modification route. a) LTBA, THF, 0 °C to r.t., 4 h, 64%; b) MsCl, py, DMAP, 0 °C to r.t., 15 h, 74%; c) O_3, CH_2Cl_2, –78 °C, then DMS, –78 °C for 30 min, 2 h to r.t., 30% **5.118** and 34% **5.119**.

We swapped the conditions by applying Lemieux-Johnson conditions as a two step procedure gave the desired ketone **5.118** in a similar yield as shown in Scheme 5.11. The elimination of both mesyl functions yielded the bis-olefin **5.120** in an impure manner. In summary, the novel route was successfully applied and the targeted compound could be synthesized. However, this route led as well to a disappointing overall yield.



Scheme 5.11: Alternative route *via* oxidative cleavage. a) OsO_4, NMO, *t*-BuOH/H_2O (4:1), 0 °C to r.t., 2.3 d, 95%; b) $NaIO_4$, THF/H_2O (2:1), r.t., 2.5 h, 52%; c) LiBr, Li_2CO_3, DMF, 140 °C, 4 h, 74%.

An advanced cyclohexadiene would shorten the route by far, since elimination events could be omitted. We envisioned the reported *ipso*-methylated cyclohexadiene carboxylic acid **5.121** might be a suitable testing candidate (Scheme 5.12).[359] The carboxylic acid derivative **5.121** was condensed under Steglich esterification conditions[360] to the allylic alcohol **4.52**, yielding the ester **5.122** in 75%. EDC x HCl was superior to other tested coupling reagents (DCC,[361] TBTU), due to SiO_2-column purification issues. The planned Claisen-rearrangement should then proceed *via* the enolether

[359] K. Vorndran, T. Linker, *Angew. Chem. Int. Ed*. **2003**, *42*, 2489.

[360] B. Neises, W. Steglich, *Angew. Chem. Int. Ed*. **1978**, *17*, 522.

[361] A. K. Perepogu, D. Raman, U. S. N. Murty, V. J. Rao, *Bioorganic Chemistry* **2009**, *37*, 46.

5.123.[362] The methods are somewhat limited for this transformation and are based mostly on low valent titanium species.[363] Wittig and other olefination conditions are working well on aldehydes and ketone, but not on ester[364] or amide moieties, due to their resonance stability. Furthermore, olefination conditions are of basic nature, whereas the oxophilic titanocene reagent[365] forms a Schrock carbene intermediate, which makes an carbonyl attack more feasible. Methylenation of the sterically demanding ester **5.122** led to no conversion for Tebbe's, Takai-Utimoto's or Lombardo's conditions.[363b-d] Treating the ester **5.122** with the freshly prepared Petasis reagent[366] formed *in situ* the instable enolether **5.123**,[367] which was purified over basic alumina. The enolether **5.123** was then directly used for the Claisen-rearrangement yielding the desired rearranged product **5.124** in a diastereomeric ratio of 9:1 and a low yield of 10% (over two steps). The enolether **5.123** seems to be unstable as well as sterically not favored due to the adjacent methyl group.

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[362] J. S. Swenton, D. Bradin, B. D. Gates, *J. Org. Chem*. **1991**, *56*, 6156.

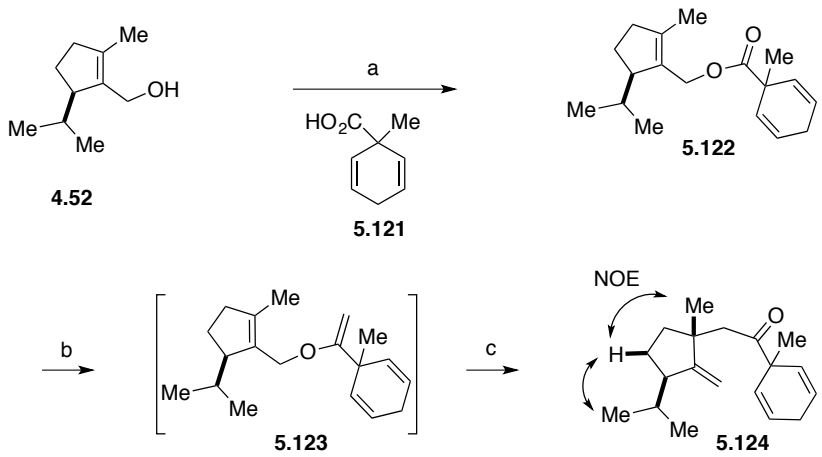
[363] a) N. A. Petasis, E. I Bzowej, *J. Am. Chem. Soc*. **1990**, *112*, 6392; b) F. N. Tebbe, G. W. Parshall, G. S. Reddy, *J. Am. Chem. Soc*. **1978**, *100*, 3611; c) T. Okazoe, K. Takai, K. Oshima, K. Utimoto, *J. Org. Chem.* **1987**, *52*, 4410; d) L. Lombardo, *Tetrahedron Lett.* **1982**, *23*, 4293; e) Y. Horikawa, M. Watanabe, T. Fujiwara, T. Takeda, *J. Am. Chem. Soc*. **1997**, *119*, 1127; f) K. A. Brown-Wensley, S. L. Buchwald, L. Cannizzo, L. Clawson, S. Ho, D. Meinhardt, J. R. Stille, D. Straus, R. H. Grubbs, *Pure Appl. Chem*. **1983**, *55*, 1733.

[364] For applications in total synthesis see: a) H. C. Kolb, S. V. Ley, A. M. Z. Slawin, D. J. Williams, *J. Chem. Soc., Perkin Trans. 1*, **1992**, 2735; b) A. B. Smith, III, K. Basu, T. Bosanac, *J. Am. Chem. Soc*. **2007**, *129*, 14872; c) D. C. Harrowven, M. C. Lucas, P. D. Howes*, Tetrahedron Lett*. **1999**, *40*, 4443.

[365] For a review see: a) R. C. Hartley, G. J. McKiernan, *J. Chem. Soc., Perkin Trans. 1*, **2002**, 2763; b) R. C. Hartley, J. Li, C. A. Main, G. J. Kiernan, *Tetrahedron* **2007**, *63*, 4825.

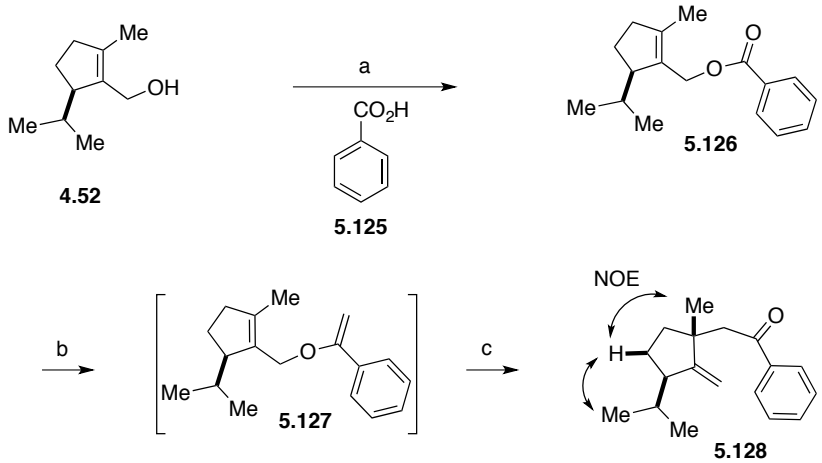
[366] J. F. Payack, D. L. Hughes, D. Cai, I. F. Cottrell, T. R. Verhoeven, *Org. Synth*. **2002**, *79*, 19.

[367] NMR-measurements were not possible due to decomposition into the allylalcohol **4.52** and acetophenon, nevertheless this indirectly proofed that enolether **5.123** was indeed formed.



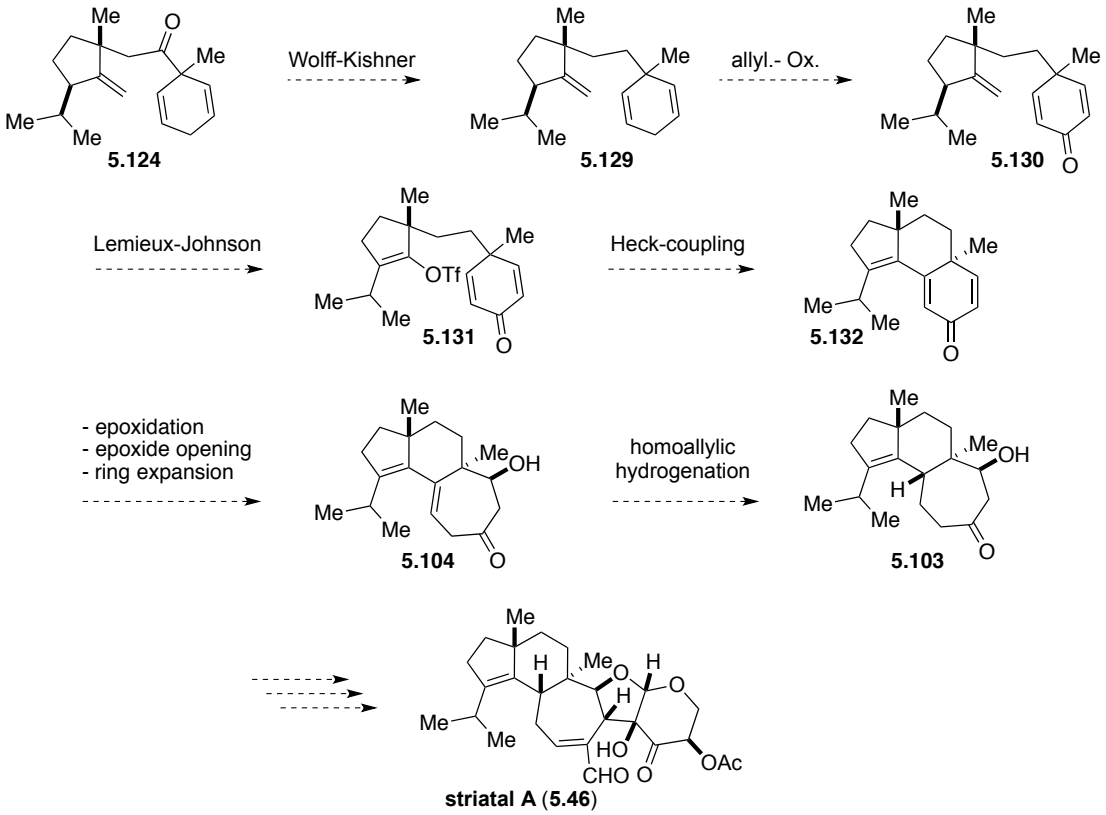
Scheme 5.12: Claisen rearrangement with an advanced cyclohexadiene moiety. a) **5.121**, EDC x HCl, DMAP, CH_2Cl_2, 0 °C to r.t., 15 h, 82%; b) Petasis reagent, Cp_2TiCl_2 (cat.), THF, 65 °C, 22 h, 30%; c) toluene, 110 °C, 19 h, 44%, d.r. = 9:1.

This hypothesis was tested by using benzoic acid (**5.125**) as a less bulky substrate. The benzoic acid ester **5.126** was obtained in 87% yield from allylalcohol **4.52** and directly subjected to the used methylenation conditions (Scheme 5.13). The benzoic enolether **5.127** was obtained in a quantitative yield. The Claisen rearranged product **5.128** was received with 77% yield (over two steps from benzoic enolether **5.127**). The diastereomeric ratio was 13:1 for the desired diastereomer **5.128**.



Scheme 5.13: Test reaction with an aromatic moiety. a) benzoic acid (**5.125**), EDC x HCl, DMAP, CH_2Cl_2, 0 °C to r.t., 22 h, 87%; b) Petasis reagent, Cp_2TiCl_2 (cat.), THF, 65 °C, 13 h, quant.; c) toluene, 110 °C, 19 h, 79%, d.r. = 13:1.

To summarize, the initial attempt following an established procedure applied on our substrate showed remarkable differences in terms of reactivity and chemical behavior. Modifications following a more convergent synthetic approach did not show the expected improved reactivity. The future planned steps for this for this route is shown in Scheme 5.14. After the Claisen-rearrangement, the ketone function of **5.124** should be removed to the alkane **5.129**.[368] An allylic oxidation[347] should furnish the enone system **5.130**, which is then transformed to the vinyltriflate[369] **5.131**. The vinyltriflate **5.131** is subjected to Heck-cyclization conditions yielding the tricycle **5.132**. Upon ring expansion[370] to the seven-membered ring **5.104** and a hydroxy directed homoallylic hydrogenation[371] should take place and give rise to the access of cyathane core structure **5.103**. The pentose will then be installed and finally lead to the natural product striatal A (**5.46**)



Scheme 5.14: Planned route towards the cyathane structure and striatal A (**5.46**).

[368] M. E. Furrow, A. G. Myers, *J. Am. Chem. Soc*. **2004**, *126*, 5436.

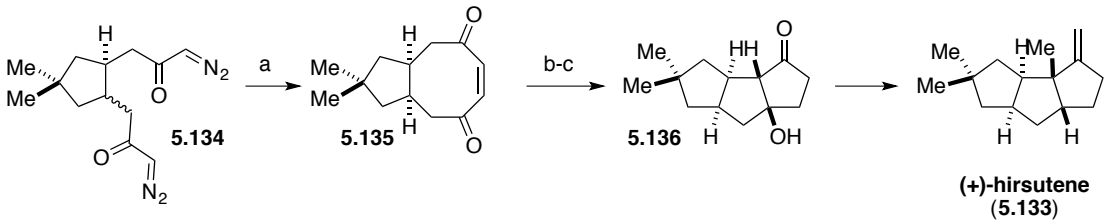
[369] M. C. Willis, C. K. Claverie, *Tetrahedron Lett*. **2011**, *42*, 5105.

[370] E. J. Kantorowski, M. J. Kurth, *Tetrahedron* **2000**, *56*, 4317.

[371] H. Watanabe, M. Nakada, *Tetrahedron Lett*. **2008**, *49*, 1518.

5.5.1.2 Diazo Approach

Facing the seven-membered ring as the challenging part in the synthesis, we envisioned a new strategy, which should directly form the seven-membered ring *via* a ring expansion reaction as earlier planned. The group of List reported an interesting macrocyclization in their total synthesis of (+)-hirsutene (**5.133**, Scheme 5.15).[372] Starting from bis-diazoketone **5.134** a Ru-mediated intramolecular carbene-carbene cyclization[373] furnished the eight-membered macrocyle **5.135**. An intramolecular *trans*-annulation afforded the 5-5-5 tricycle **5.136** and further manipulation yielded the natural product (+)-hirsutene (**5.133**).

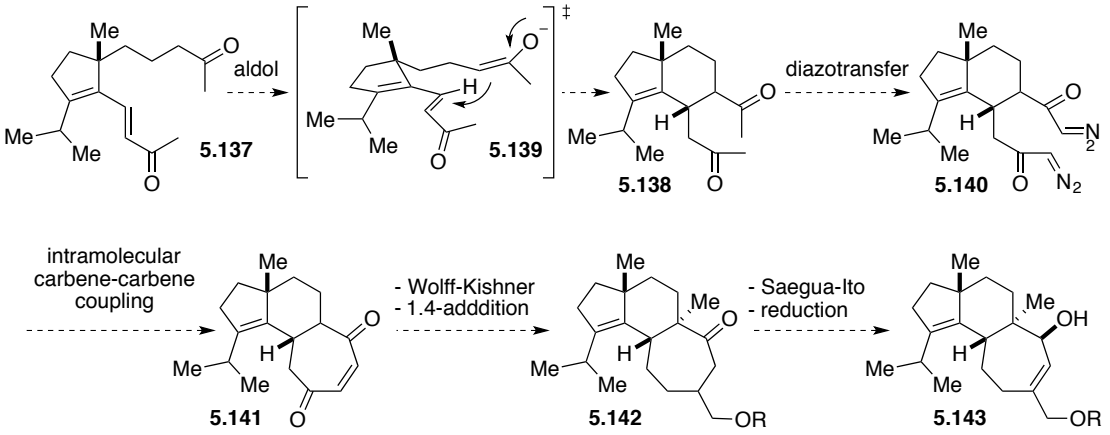


Scheme 5.15. List's intramolecular carbene-carbene cyclization in the synthesis of (+)-hirsutene (**5.133**). a) $Ru(\eta^5\text{-}C_5H_5)(PPh_3)_2$ (cat.), CH_2Cl_2, 55 °C, 52%; b) H_2, Pd/C, EtOAc, 91%; c) *trans*-4-fluoro proline, DMSO, r.t., 15 h, 84%.

This strategy can be applied on our system by targeting the diketone **5.137** (Scheme 5.16). The six-membered ring **5.138** is obtained after an intramolecular aldol reaction on the enone **5.139**. A chiral catalyst such as proline can be used if the aldol reaction is not fully substrate controlled. A diazotransfer on both ketone moieties would furnish the diazocompound **5.140**, which forms upon intramolecular carbene-carbene cyclization the desired 5-6-7-tricycle **5.141**. Further manipulation on the seven membered ring furnishes the ketone **5.142**, which is converted into the cyathane scaffold **5.143**.

[372] C. L. Chandler, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 6737.

[373] A. Del Zotto, W. Baratta, G. Verardo, P. Rigo, *Eur. J. Org. Chem*. **2000**, 2795.



Scheme 5.16: Proposed synthetic pathway *via* an intramolecular carbene-carbene coupling reaction towards the cyathane core structure **5.143**.

Starting from the same sequence, the aldehyde **4.54** was subjected to an HWE reaction to form the α,β-unsaturated ketone **5.144** (Scheme 5.17). Reductive attempts on the enone **5.144** to form the saturated ketone **5.145** were not successful using Hantzsch ester[374] or Raney-Ni[375] conditions. Lipshutz's modified Stryker reagent delivered the ketone **5.145** in a clean reaction and a good yield.[376] Epoxidation of the olefin **5.145** gave the epoxide **5.146**, which upon SiO_2-column purification directly gave the desired allylic alcohol **5.147** in 71% yield. Oxidation in the presence of DMP afforded the unsaturated aldehyde **5.148** in a good yield of 70%. The same conditions as aforementioned were applied for the HWE homologation to yield enone **5.149** but the aldehyde **5.148** was completely inert to the used conditions. The phosphonate was swapped the to 2-oxopropyltriphenylphosphonium chloride and NaHMDS as the base, but also under this conditions only the starting material was recovered. Aldol condensation reaction with base (LDA,[377] sodiumethoxide[378] or piperidine/AcOH[379]) and acetone gave no reaction.

[374] D. B. Ramachary, M. Kishor, *J. Org. Chem*. **2007**, *72*, 5056.

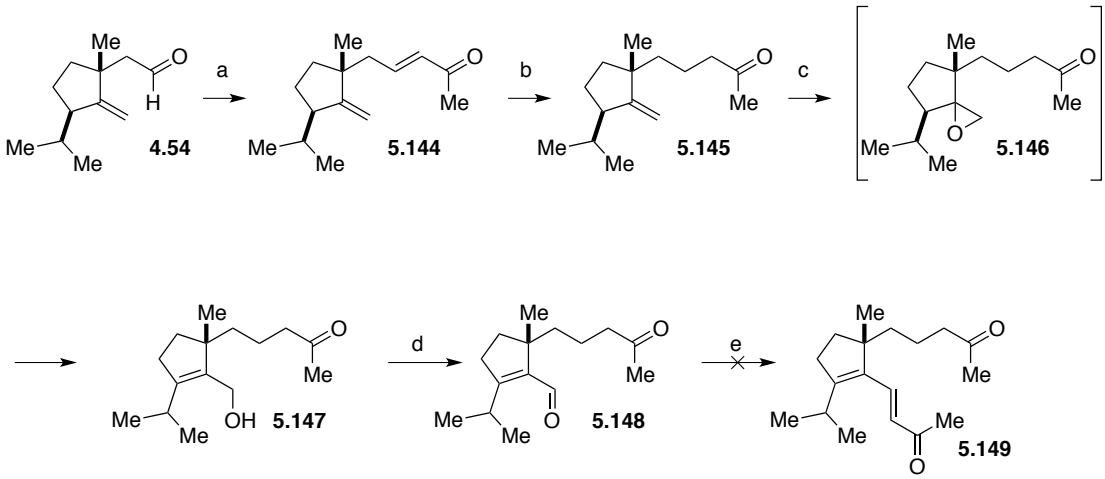
[375] A. F. Barrero, E. J. Alvarez-Manzaneda, R. Chaboun, A. R. Rivas, P. L. Palomino, *Tetrahedron* **2000**, *56*, 6099.

[376] B. A. Baker, Z. V. Bošković, B. H. Lipshutz, *Org. Lett*. **2008**, *10*, 289.

[377] P. Kraft, S. Jordi, N. Denizot, I. Felker, *Eur. J. Org. Chem*. **2014**, 554.

[378] C. Chapius, R. Brauchli, *Helv. Chim. Acta* **1993**, *76*, 2070.

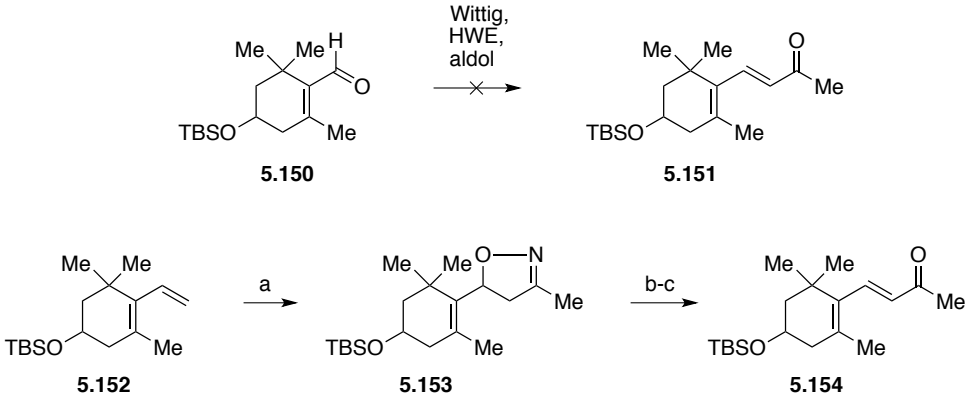
[379] A. Srikrishna, B. Beeraiah, *Tetrahedron: Asymmetry* **2007**, *18*, 2587.



Scheme 5.17: Revised strategy approach for the synthesis of the diazo precursors **5.149**. a) dimethyl 2-oxopropylphosphonate, DIPEA, LiCl, ACN, 5 h, 79%; b) 1,2-bis(diphenylphosphino)benzene, $Cu(OAc)_2$ x H_2O, PMHS, *t*-BuOH, r.t., 3 h, 80%; c) *m*-CPBA, CH_2Cl_2, 0 °C to r.t., 4 h, 71%; d) DMP, CH_2Cl_2, r.t., 19 h, 70%; e) dimethyl 2-oxopropylphosphonate, DIPEA, LiCl or 2-oxopropyltriphenylphosphonium chloride, NaHMDS or LDA, or acetone and NaOEt, or acetone and piperidine/AcOH.

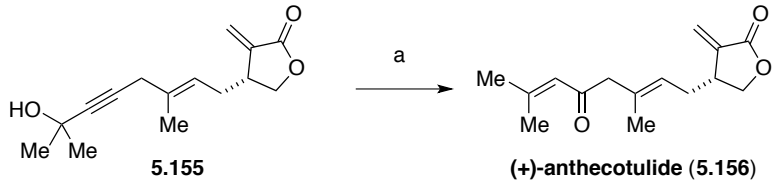
The group of Shishido faced this problem as well upon attempts *via* a Wittig reaction on a hindered aldehyde **5.150** as shown in Scheme 5.18.[380] The sterically demanding aldehyde **5.150** was not reactive under standard homologation conditions such as Wittig or HWE reaction to yield the desired enone **5.151**. The homologation was solved *via* a nitrile oxide–alkene [3 + 2] cycloaddition on a terminal olefin **5.152**. The formed isoxazoline **5.153** was reduced to the β-hydroxyketone and upon elimination of water the unsaturated ketone **5.154** was obtained.

[380] D. Kikuchi, M. Yoshida, K. Shishido, *Synlett* **2012**, *23*, 577.



Scheme 5.18: Homologation attempts on a sterically hindered aldehyde **5.150** and their solution *via* a nitrile oxide–alkene [3 + 2] cycloaddition approach for the synthesis of the α,β-unsaturated ketone **5.154**. a) *N*-hydroxyacetimidoyl chloride,[381] Et_3N, CH_2Cl_2, r.t.,10 h, 75%; b) H_2, Raney-Ni, $(MeO)_3B$, $MeOH/CH_2Cl_2/H_2O$ (10:5:1), r.t., 4 h, 74%; c) Ac_2O, py, DMAP, CH_2Cl_2, r.t., 5 h, then DBU, r.t., 11 h, 95%.

The approach implements a lot of additional steps, which we thought to be less elegant. The synthesis of α,β-unsaturated ketone can also be envisioned by a Meyer-Schuster rearrangement[382] of a tertiary alcohol **5.155** as shown in the synthesis of Hodgson and co-workers on their studies of (+)-anthecotulide (**5.156**, Scheme 5.19).[383]



Scheme 5.19: Meyer-Schuster rearrangement applied by the Hodgson group in their synthesis of (+)-anthecotulide (**5.156**). a) $MoO_2(acac)_2$, $AuCl(PPh)_3$, AgOTf, toluene r.t., 3h, 87%.

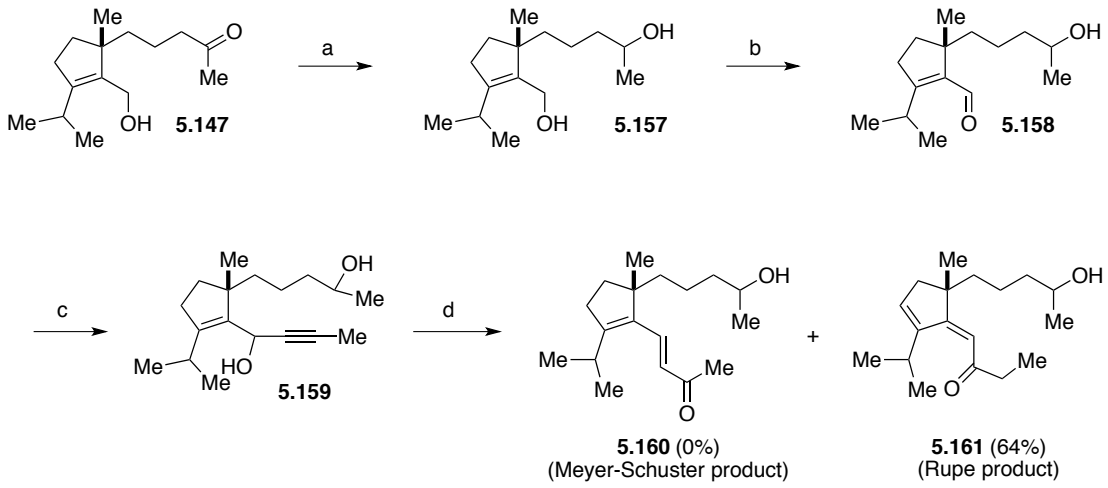
Starting from the allylic alcohol **5.147**, the ketone was reduced to the alcohol **5.157** as shown in Scheme 5.20. The allylic alcohol was regioselectively oxidized in the presence of the secondary alcohol using

[381] a) K. H. Meyer, K. Schuster, *Chem. Ber*. **1922**, *55*, 819; b) Z. Zhang, D. P. Curran, *J. Chem. Soc., Perkin Trans. 1* **1991**, 2627.

[382] D. A. Engel, G. B. Dudley, *Org. Biomol. Chem*. **2009**, *7*, 4149.

[383] D. A. Hodgson, E. P. A. Talbot, B. P. Clark, *Org. Lett*. **2011**, *13*, 5751.

Barium manganate(VI) to aldehyde **5.158** in 64% yield. MnO_2[384] proved to be not successful on this hindered allylic alcohol **5.157** and only starting material was recovered. The regioselective oxidation was not always reproducible, yielding in no conversion or oxidation of the secondary alcohol instead of the allylic alcohol. A HWE condition was applied on the aldehyde **5.158**, but no conversion was observed. Treating the aldehyde **5.158** with a combination of LDA and 1,2-dibromopropane forming *in situ* the lithiated 1-propynyl species, which subsequently added to the aldehyde forming the 1-propynyl alcohol **5.159**. Several methods were tested for the Meyer-Schuster rearrangement, to our disappointment, not the Meyer-Schuster rearranged product **5.160** was obtained, but the known side reaction took place forming the Rupe rearranged product **5.161**.[385]



Scheme 5.20: Preparation attempts for the synthesis of the diazo precursor **5.140**. a) $LiAlH_4$, THF, 0 °C, 1 h, quant.; b) $BaMnO_4$, CH_2Cl_2, r.t, 19 h, 64%; c) 1,2-dibromopropane, LDA, -78 °C to r.t., then –78 °C, **5.158**, –78 °C to r.t., 17 h, 85%; d) $Cu(OTf)_2$, CH_2Cl_2/EtOH (4:1), r.t., 2.5 h**.**

The side reaction could not be circumvented by applying several Lewis-acids such as $Sc(OTf)_3$,[386] $Cu(OTf)_2$ or $InCl_3$[387]. We were quite surprised about these findings, because normally the Rupe side reactions takes place *via*

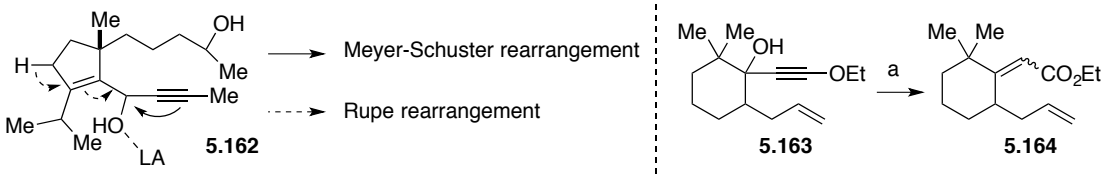
[384] N. Kato, K. Nakanishi, H. Takeshita, *Bull. Chem. Soc. Jpn*., **1986**, *59*, 1109.

[385] S. Swaminathan, K. V. Narayanan, *Chem. Rev*. **1971**, *71*, 429.

[386] D. A. Engel, S. S. Lopez, G. B. Dudley, *Tetrahedron* **2008**, *64*, 6988.

[387] V. Cadierno, J. Francos, J. Gimeno, *Tetrahedron Lett*. **2009**, *50*, 4773.

elimination of the adjacent β-hydrogen,[388] which is in our case not present. However, δ-hydrogens are present and eliminated faster than the 1,3-allylic shift took place (**5.162**, Scheme 5.21 left). A common strategy is the installation of electron-donating-groups on the terminal alkine position, which favor the 1,3-allylic hydroxy shift. De Mesmaeker and co-workers used this method in their synthesis of 5-deoxystrigol, an intermediate in the biosynthesis of strigolactones (plant hormones, Scheme 5.21).[389] Installation of an ethoxygroup on alkyne **5.163** furnished the desired unsaturated ester **5.164**. In our case, the resulting ester would need to be manipulated further and a double diazotransfer as it was planned might not be straightforward anymore. We therefore searched for alternative approaches.



Scheme 5.21: Competing Rupe and Meyer-Schuster rearrangements (left, LA = Lewis acid) and installation of an electron-donating-group to force the Meyer-Schuster reaction (right). a) $Sc(OTf)_3$ (5 mol%), CH_2Cl_2, EtOH, 82%, E:Z = 1:1; or $AuCl_3$ (5 mol%), CH_2Cl_2, EtOH, 90%.

The installation of an α,β-unsaturated ketone moiety can be achieved by installation of an allyl group and further oxidations on the terminal olefin. We started from the ketone **5.145** and reduced it to the alcohol **5.165** and protected the secondary alcohol **5.166** with a TBS-group to yield the protected secondary alcohol **5.166** (Scheme 5.22). The epoxidation of the terminal olefin **5.166** led to a stable epoxide **5.167** this time and did not open spontaneously to the desired allylic alcohol **5.168**. Base promoted epoxide isomerization (LDA,[390] LiTMP,[391] DATMP[392]) showed only recovery of the epoxide **5.167**. Treating the epoxide **5.167** with TMSOTf and DMAP gave the

[388] G. F. Hennion, R. B. Davis, D. E. Maloney, *J. Am. Chem. Soc*. **1949**, *71*, 2813.

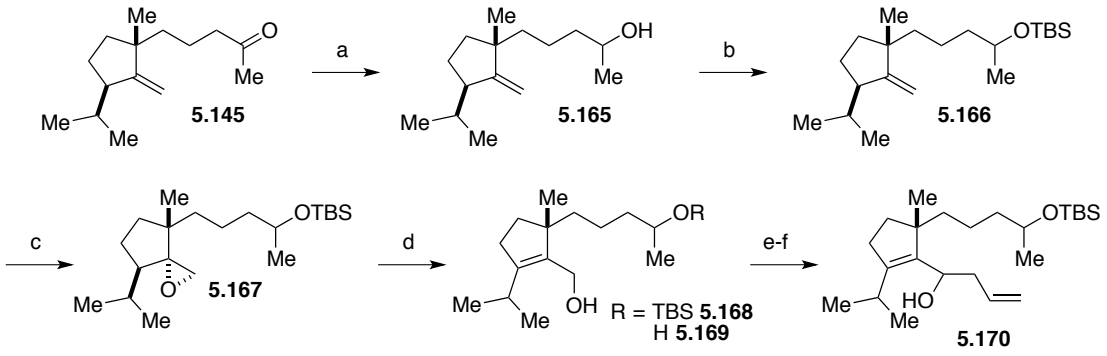
[389] M. Lachia, P.-Y. Dakas, A. De Mesmaeker, *Tetrahedron Lett.* **2014**, *55*, 6577.

[390] Y. Ma, D. B. Collum, *J. Am. Chem. Soc*. **2007**, *129*, 14818.

[391] S. H. Wiedemann, A. Ramírez, D. B. Collum, *J. Am. Chem. Soc*. **2003**, *125*, 15893.

[392] A. Yasuda, S. Tanaka, K. Oshima, H. Yamamoto, H. Nozaki, *J. Am. Chem. Soc*. **1974**, *96*, 6513.

allylic alcohol **5.168** in 19%. Improved epoxide opening yields could be obtained in the presence of the acidic Amberlyst IR-120 resin. The allylic alcohol **5.168** and TBS cleaved product **5.169** was obtained in yields ranging from 28% to 81%. We therefore subjected the epoxide to milder acidic conditions using SiO_2 and were pleased to see that the allylic alcohol **5.168** was slowly formed keeping the TBS protecting group intact. By simply heating the reaction to reflux, the epoxide **5.167** fully opened to the desired allylic alcohol **5.168** within a few hours in 67% yield. Oxidation of the allylic alcohol **5.168** to the unsaturated aldehyde gave only moderate yields of 43% in the presence of DMP and no conversion using IBX. A reasonable amount was achieved using pyridinium chromate, and the crude material was directly used in the next step. The allylation gave the desired secondary alcohol **5.170** in a yield of 62% (over two steps).



Scheme 5.22: Alternative approach towards the diazo precursor **5.170**. a) $LiAlH_4$, THF, 0 °C, 1.2 h, 79%; b) TBSOTf, 2.6-lutidine, CH_2Cl_2, −20 °C to r.t., 14 h, 95%; c) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C to r.t., 19 h, 80%; d) SiO_2, EtOAc, 105 °C, 24 h, 67%; e) pyridinium dichromate, CH_2Cl_2, r.t., 3.5 h; f) allylmagnesiumbromide, THF, −78 °C to r.t., 1 h, 62% (over two steps).

With the homoallyl alcohol **5.170** in hand a Wacker-type-oxidation was performed on the terminal olefin (Scheme 5.23).[393] A catalytic method was described by Kaneda and co-workers using $PdCl_2$, DMA and molecular oxygen as the oxidant to perform the Wacker-type-oxidation to furnish the

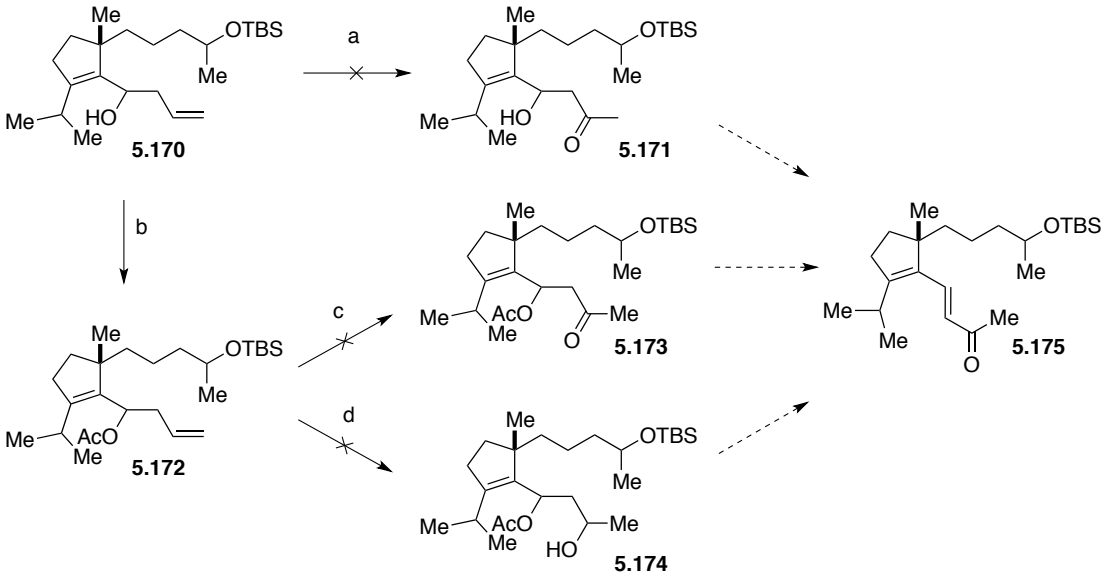
[393] A. B. Smith, III, G. K. Friestad, J. J.-W. Duan, J. Barbosa, K. G. Hull, M. Iwashima, Y. Qiu, P. Grant Spoors, E. Bertouneaque, B. A. Salvatore, *J. Org. Chem*. **1998,** *63*, 7596.

ketone **5.171**.[394] To our disappointment, no reaction occurred on our substrate. Assuming that the free hydroxy group might coordinate to the Pd-species and is shutting down any further reactions, we applied a described method suitable for challenging substrates.[395] Furthermore, this method can overcome regioselectivity issues, which are observed when hydroxy groups or protecting groups are still able to coordinate to the Pd-species and the attack of water attacks both position of the olefin forming Markovnikov and anti-Markovnikov products. TBHP is therefore used in combination with a bidendate ligand to prevent a free hydroxy function to coordinate to the Pd-species. To our disappointing, no reaction occurred on the free hydroxy substrate **5.170**. As described, an acetylation might be helpful and the acetyl group was installed with Ac_2O and triethylamine afforded the protected alcohol **5.172** in a yield of 80%. The same conditions were again applied, but to our disappointment the desired ketone **5.173** was not obtained. The terminal olefin is probably too shielded from the surround making a general attack of multiple reagents not suitable. Another method is the hydroxymercuration, which should deliver the hydroxy function in a Markovnikov fashion.[396] The acetylated substrate **5.172** was subjected to hydroxymercuration condition, but the persistent bright yellow reaction mixture already indicated that the $Hg(OAc)_2$ was not consumed and therefore the secondary alcohol **5.174** not formed. The terminal olefin might be not accessible for the desired transformation and we did not further investigated on this synthetic approach towards intermediate **5.175**.

[394] T. Mitsudome, T. Umetani, N. Nosaka, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, *Angew. Chem. Int. Ed.* **2006**, *45*, 481.

[395] B. W. Michel, A. M. Carmelio, C. N. Cornell, M. S. Sigman, *J. Am. Chem. Soc*. **2009**, *131*, 6076.

[396] C. Singh, M. Hassam, V. P. Verma, A. S. Singh, N. K. Naikade, S. K. Puri, P. R. Maulik, R. Kant, *J. Med. Chem*. **2012**, *55*, 10662.



Scheme 5.23: Synthetic attempts towards the α,β,γ,δ-unsaturated ketone **5.175**. a) $AgSbF_6$, Pd(quinox)Cl_2, *t*-BuOOH, CH_2Cl_2, r.t., 16 h; b) Et_3N, Ac_2O, DMAP, CH_2Cl_2, 0 °C, 1 h, then r.t., 30 min, 80%; c) $AgSbF_6$, Pd(quinox)Cl_2, *t*-BuOOH, CH_2Cl_2, r.t., 20 h; d) $Hg(OAc)_2$, $NaBH_4$, THF, H_2O, r.t., 1.5 h.

5.6 Conclusion

In the course towards the total synthesis of the natural product striatal A (**5.46**), various synthetic aspects were evaluated. Striatal A (**5.46**) represents a highly complex diterpenoid with a cyathane core structure and an attached pentose unit. The 5-6-7-membered ring moiety is in close relation to our previous studies in the natural product cyrneine A (**5.91**). A modified strategy should furnish the core structure of the striatal family. Starting from (*S*)-limonene (**4.50**), the 5-ring motif was achieved following a reported procedure involving a Favorskii ring contraction reaction and a Dieckmann condensation. An Eschenmoser-Claisen rearrangement installed the first quaternary center, bearing a methyl group, in a diasteromeric ratio of 24:1. Surprisingly, the established methodology was not suitable anymore in the next steps. In general the desired products could be achieved in low yields for the first few initial steps of the project. Furthermore, the methods were dominated by side reactions, which made further steps not suitable towards a total synthesis. A reason might be the influence of the 5-ring junction as well as steric hindrance of other groups.

Therefore, a novel strategy was elaborated to build up the 5-6-7-membered ring motif *via* an intramolecular carbene-carbene cyclization, which would give access to an already highly functionalized 7-ring motif. However, a sterically demanding aldehyde made further reactions towards a C2-homolagtion under HWE conditions not feasible. More harsh conditions were applied by reaction of the aldehyde **5.158** with an organolithium species and the expected prop-1-yne product was indeed obtained. We envisioned applying a Meyer-Schuster rearrangement, but the rearrangement gave exclusively the Rupe rearranged product **5.161**, which made further progress impossible.

Other attempts, on a homoallylic alcohol moiety **5.170** were not fruitful, due to the unreactivity of the terminal olefin towards the applied Wacker-oxidation conditions and oxymercuartion conditions. We therefore stopped our progress towards the total synthesis of striatal A (**5.46**), due to not promising preliminary results.

6 Conclusion

This thesis entitled “Total Syntheses of (–)-Fragin and Valdiazen, and Synthetic Studies Towards Complex Neuritogenic Terpenoids” describes the synthesis of biologically active natural products for different mankind diseases, malaria, neurodegeneration, and bacterial infection. Each chapter gives an overview of the respective disease and describes the classes of natural products that have been developed as potential treatment so far.

Chapter one highlights the “golden era” of natural products in drug discovery over the last decade. From early treatments as antibiotics over chemotherapeutic agents, the chapter includes as well an outlook for a new “golden era” of natural products.

Chapter two updated synthetic and biological aspects of the natural product fragin. In a first step, we achieved an enantioselective synthesis of both fragin enantiomers in eight steps and 13% overall yield and determined the chiral center to be (*R*)-configured. In a second step, a racemic intermediate in the biosynthesis of fragin was isolated and named valdiazen. The biosynthetic intermediate was confirmed both using analytical techniques and chemical synthesis. SAR-studies on fragin indicated that the diazeniumdiolate motif is responsible for antibacterial activity and that the chiral center has no influence. Fragin is active against Gram-positive and only poorly active against Gram-negative bacteria, whereas the biosynthetic intermediate is inactive in both cases.

Chapter three aimed at providing a synthetic route for the total synthesis of the natural product (2*R*)-hydroxynorneomajucin. The synthesis featured a manganese-induced 6-*endo-trig* cyclization and a regiospecific C-H activation of a sp^3-center. The outlook provides further strategies for the insertion of the last missing hydroxy function on an advanced intermediate towards the total synthesis of (2*R*)-hydroxynorneomajucin. Furthermore, two *nor*-type

sesquiterpene structures, namely 3,4-dehydro-norneomajucin and (1*S*)-2-oxo-3,4-dehydronorneomajucin of known neurite outgrowth inducing sesquiterpenes could be successfully achieved in 16 respectively 17 steps and their activity profile will be evaluated.

Chapter four evaluated the potency of a novel antimalarial agents. The spontaneous formation of endoperoxides had been discovered by serendipity on our synthetic efforts towards the total synthesis of striatal A (chapter five). The reaction was then used to access a wide array of antiplasmodial endoperoxides. The synthesis featured a manganese(III) mediated peroxide formation via a formal [2 + 2 + 2] cycloaddition. SAR-studies on the endoperoxidal skeleton revealed that conformational as well as the free hydroxy-endoperoxide structure play a crucial role for antiplasmodial activity. The synthetic strategy allows obtaining further endoperoxidal structures by changing the starting material or by using late stage-modifications.

Chapter five showed synthetic studies on the natural product striatal A. Our initial synthetic strategy proved not be suitable, mainly due to steric hindrance of an intermediate. A newly elaborated strategy led to an advanced intermediate, however, its unreactivity or formation of by-products made further progress on this route impossible. A novel approach has to be considered towards the total synthesis of striatal A.

7 Experimental Part

7.1 General Methods and Material

General Reactions were carried out using oven-dried glassware under an atmosphere of dry Ar or N_2 and magnetically stirred, unless noted otherwise. Air- and moisture-sensitive liquids and solutions were transferred *via* syringe or stainless steel canula.

Reagents were purchased from commercial suppliers (Acros, Sigma-Aldrich) and used without further purification, unless noted otherwise.

Solvents (methylene chloride, diethylether, tetrahydrofuran, acetonitrile, toluene) for reactions were purified by filtration and dried by passage over activated anhydrous neutral A-2 alumina (Innovative Technology solvent drying system) under an atmosphere of dry nitrogen. Methanol (analytical grade) was used as received. Analytical grade solvents were used as received for extractions and chromatographic purifications. Deuterated-solvents were purchased from Cambridge Isotope Laboratories, Inc. (Andover, MA, USA). Work-up was performed with dist. solvents.

Thin Layer Chromatography was used for monitoring reactions and carried out using Merck silica gel 60 F_{254} plates, visualized with UV light or developed either with aqueous cerium ammonium molybdate (CAM) stain solution followed by heating.

Flash Chromatography was performed using Silicycle SiliaFlash® P60 (230-400 Mesh) at a pressure of *ca.* 0.3 bar. Eluents and R_f are indicated.

^{1}H NMR spectra were recorded on Varian Gemini Bruker DPX 400 MHz, Bruker Avance II 400 MHz NMR, Bruker Avance II 500 MHz NMR or Bruker

Avance I 600 MHz NMR spectrometer at 298K in the indicated deuterated solvent, unless otherwise stated. Data are reported as follow: chemical shift (δ, ppm), multiplicity (s, singulet; d, doublet; dd, doublet of doublets; dt, doublet of triplets; t, triplet, q, quartett, quin., quintet, m, multiplet or not resolved signal), coupling constant (*J,* Hz) and integration. All signals were referenced to the internal solvent signal as standard ($CDCl_3$, δ = 7.26; MeOD, δ = 3.31).

^{13}C NMR spectra were recorded with ^{1}H-decoupling on Varian Gemini 101 MHz spectrometer at 298K in the indicated deuterated solvent, unless otherwise stated. All signals were referenced to the internal solvent signal as standard ($CDCl_3$, δ = 77.16; MeOD, δ = 49.00).

IR spectra were recorded on a Varian 800 FT-IR ATR spectrometer or ona Spectrum Two (UATR) FT-IR Spectrometer (Perkin Elmer). Data are reported in terms of frequency of absorption ($\tilde{\nu}$, cm^{-1}).

Optical rotations $[\alpha]_D^T$ were measured at the sodium D line using a 1 mL cell with a 1 dm path length on a Jasco P-2000 digital polarimeter and the concentration *c* is given in g/100mL in the indicated solvent.

Mass spectra: Were recorded on a QTOF-ESI spectrometer (bruker maXis 4G) or on a QExactive instrument (Thermo Fisher Scientific, Bremen, Germany) equipped with a heated electrospray (ESI) ionization source and connected to a Dionex Ultimate 3000 UHPLC system.

Melting points (Mp) were determined using a Büchi B-545 apparatus in open capillaries and are uncorrected.

X-ray analyses: University of Basel; data collections for all crystal structures were performed at low temperature (123 K) using Mo$K\alpha$ or Cu$K\alpha$ radiation on a Bruker Kappa APEX diffractometer. Integration of the frames

and data reduction was carried out using the APEX2 software.[397] The structures were solved by direct methods using SIR92.[398] All non-hydrogen atoms were refined anisotropically by full-matrix least-squares on F using CRYSTALS.[399] Univeristy of Zurich: All measurements were made on an *Agilent Technologies SuperNova* area-detector diffractometer[400] using Cu *K*a radiation (*l* = 1.54184 Å) from a micro-focus X-ray source and an *Oxford Instruments Cryojet XL* cooler. Data reduction was performed with *CrysAlisPro*. [400] The structure was solved by direct methods using *SHELXS-2013.*[401]

Fluorescence spectroscopy was measured on a Shimadzu 5301 PC spectrofluorophotometer.

[397] Bruker Analytical X-ray Systems, Inc., 2006. *Apex2*, Version 2 User Manual, M86-E01078, Madison, WI.

[398] A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst.* **1994**, *27*, 435.

[399] P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Cryst*. **2003**, *36*, 1487.

[400] *CrysAlisPro*, Version 1.171.3, Agilent Technologies, Yarnton, Oxfordshire, England, **2014**.

[401] G.M. Sheldrick, *Acta Crystallogr. Sect. A*, **2008**, *64*, 112.

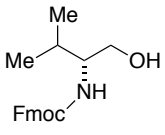
7.2 Total Syntheses and SAR-Studies on (−)-Fragin and Valdiazen

Preparation and analytical data for intermediates (**2.97b** and **2.98b**) and precursors for the ammonium salts **2.132a-d** were reported by Liskamp and co-workers.[92]

General procedure for the carboxylic acid to alcohol reduction:[92]

Fmoc-protected amino acid (14.5 mmol, 1.0 eq) was dissolved in DME (28 mL) and cooled to −15 °C. *N*-Methylmorpholine (14.5 mmol, 1.0 eq) and isobutyl chloroformiate (14.5 mmol, 1.0 eq) was added and the mixture stirred at −15 °C for 1.5 h. The suspension was filtered and the filter cake was washed with DME (10 mL). The filtrate was cooled to −15 °C and a solution of $NaBH_4$ (21.8 mmol, 1.5 eq) in water (7.0 mL) was added in one portion and the mixture diluted with water (350 mL). The mixture was cooled to 0 °C and the white precipitate was filtered off and washed with water (3 x 10 mL) and pentane (2 x 15 mL). The white solid was dried at the rotavapor (70 °C, 35 mbar) to yield the pure alcohol as a white solid.

(9*H*-fluoren-9-yl)methyl-(*R*)-(1-hydroxy-3-methylbutan-2-yl)carbamate (2.97a):

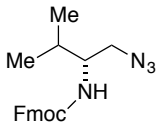


White solid (14.1 mmol, 98%, from **2.96a**); **Optical rotation:** $[\alpha]_D^{25}$ = +19.4 (*c* 1.02, $CHCl_3$). The data were in good agreement with the reported.[92]

General procedure for the Mitsunobu reaction:

Alcohol (32.2 mmol, 1.0 eq) and PPh_3 (64.4 mmol, 2.0 eq) were dissolved in dry THF (260 mL) and cooled to 0 °C. DEAD (40% in toluene, 64.4 mmol, 2.0 eq) and then DPPA (64.4 mmol, 2.0 eq) were added and the mixture allowed to warm to r.t. over 3 h. The mixture was evaporated after 10 h in total. The crude was purified by flash column chromatography (pentane/EtOAc 8:1 to 2:1) to yield the desired azide as a white solid.

(9*H*-fluoren-9-yl)methyl (*R*)-(1-azido-3-methylbutan-2-yl)carbamate- (2.98a):



White solid (26.9 mmol, 84%, from **2.97a**); **Optical rotation**: $[\alpha]_D^{25}$ = +22.8 (*c* 0.43, $CHCl_3$); the data were in good agreement with the reported.[92]

General procedure for the azide to ammonium salt reduction:

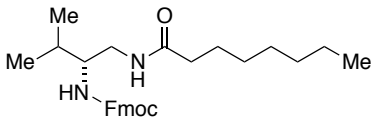
Azide (0.26 mmol, 1.0 eq) was dissolved in dry MeOH/$CHCl_3$ (1.1 mL + 0.2 mL) and stirred for 20 minutes at r.t. The mixture was cooled to 0 °C and Pd/C (10%, 28 mg, 0.1 eq) was added under an argon atmosphere, then triethylsilane (312 mg, 0.43 mL, 2.63 mmol, 10 eq) was added dropwise into the open flask. After 4 h, additional $CHCl_3$ (0.1 mL) and triethylsilane (1.32 mmol, 5 eq) were added dropwise into the open flask and stirred over night at r.t. This procedure was repeated until no more starting material was detected by TLC. The mixture was filtered over Celite and washed with MeOH and the filtrate evaporated. The residue was suspended in pentane, filtered and washed several times with pentane. The residue was dried to dryness to yield the pure ammonium salt (**2.99a-b** and **2.132a-d**), which was directly converted to fatty acids products.

General procedure for fatty acid condensation:

The ammonium salt (554 mmol, 1.0 eq) was suspended in CH_2Cl_2 (2.0 mL) and octanoyl chloride (0.61 mmol, 1.1 eq) was added. The mixture was cooled to 0 °C and DMAP (55.4 μmol, 0.1 eq) was added. A solution of DIPEA (1.11 mmol, 2.0 eq) in CH_2Cl_2 (0.8 mL) was then added. The solution was stirred for 30 minutes at 0 °C and then allowed to warm to r.t. and stirred for 14 h. The mixture was diluted with EtOAc and washed with aq. HCl (1 M, 2.0 mL), sat. aq. $NaHCO_3$ (2 x 2.0 mL) and brine (2.0 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to obtain a brownish solid. The extract was recrystallized from cyclohexane (20 mg/3 mL) at reflux for 15 minutes and then cooled to r.t. The white suspension was filtered and the residue washed with cold cyclohexane (3 x 2.0 mL) to afford the desired

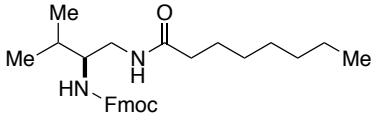
amide.

(9*H*-fluoren-9-yl)methyl (*R*)-(3-methyl-1-octanamidobutan-2-yl)carbamate (2.100a):



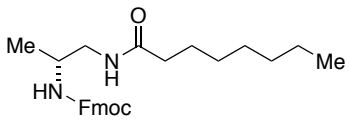
White solid (870, 1.93 mmol, 77%, from **2.99a**); **M.p.**: 128.3 – 129.0 °C; **R_f** = 0.52 (SiO_2, pentane/EtOAc 1:1); **Optical rotation**: $[\alpha]_D^{25}$ = +32.1 (*c* 0.53, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3306, 2953, 2927, 2856, 1690, 1641, 1540, 1450, 1376, 1288, 1252, 1122, 1036, 758, 734, 672 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* = 7.76 (d, *J* = 7.4 Hz, 2H), 7.58 (dd, *J* = 7.2, 4.3 Hz, 2H), 7.40 (d, *J* = 7.4 Hz, 2H), 7.31 (d, *J* = 7.5 Hz, 2H), 6.03 (bs, 1H), 5.02 (d, *J* = 8.9 Hz, 1H), 4.44 – 4.40 (m, 1 H), 4.35 – 4.31 (m, 1H), 4.22 – 4.19 (m, 1H), 3.61 – 3.54 (m, 1H), 3.48–3.41 (m, 1H), 3.29 – 3.23 (m, 1H), 2.13 (t, *J* = 7.5 Hz, 2H), 1.81 (sext, *J* = 6.5 Hz, 1H), 1.59 – 1.52 (m, 2H), 1.25 – 1.19 (m, 8H), 0.96 (t, *J* = 7.2 Hz, 6H), 0.83 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* = 174.3, 157.5, 144.0, 143.9, 141.4, 127.9, 127.9, 127.2, 125.2, 125.1, 120.1, 120,1. 67.0, 57.1, 47.4, 42.4, 36.9, 31.8, 30.9, 29.4, 29.1, 25.9, 22.7, 19.4, 18.3, 14.2; **HRMS (ESI)** m/z calcd for $C_{28}H_{39}N_2O_3$ $[M+H]^+$: 451.2955, found: 451.2957.

(9*H*-fluoren-9-yl)methyl (*S*)-(3-methyl-1-octanamidobutan-2-yl)carbamate (2.100b):



White solid (983 mg, 2.18 mmol, 94% from **2.99b**); **Optical rotation**: $[\alpha]_D^{25}$ = –32.6 (*c* 0.20, $CHCl_3$).

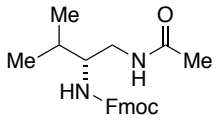
(9*H*-fluoren-9-yl)methyl-(*R*)-(1-octanamidopropan-2-yl)carbamate (2.133a):



White solid (46.4 mg, 0.11 mmol, 70%, from **2.132a**); **M.p.**: 145.2 – 145.6 °C (decomposition); **R_f** = 0.44 (SiO_2, pentane/EtOAc 1:1); **Optical rotation**: $[\alpha]_D^{25}$ = +17.0 (*c* 0.35, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3306, 2928, 2863, 1686, 1644, 1538, 1449, 1314, 1267, 1232, 1085, 1058, 736, 666 cm^{-1}; **^{1}H**

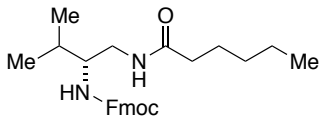
NMR (400 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 7.4 Hz, 2H), 7.58 (dd, *J* = 2.8, 7.7 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 6.10 (bs, 1H), 5.24 (d, *J* = 7.5 Hz, 1H), 4.39 – 4.32 (m, 2H), 4.20 (t, *J* = 7.2 Hz, 1H), 3.83 (bs, 1H), 3.40 – 3.33 (m, 1H), 3.28 – 3.23 (m, 1H), 2.15 (t, *J* = 7.6 Hz, 2H), 1.62 – 1.55 (m, 2H), 1.28 – 1.17 (m, 11H), 0.84 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 174.3, 156.8, 144.0, 143.9, 141.4, 127.8, 127.2, 125.2, 125.2, 120.1, 66.9, 48.0, 47.3, 45.6, 36.9, 31.8, 29.4, 29.1, 25.9, 22.7, 18.8, 14.2; **HRMS (ESI)** m/z calcd for $C_{26}H_{35}N_2O_3$ $[M+H]^+$: 423.2642, found: 423.2647.

(9*H*-fluoren-9-yl)methyl-(*R*)-(1-acetamido-3-methylbutan-2-yl)carbamate (2.137c):



White solid (845 mg, 2.31 mmol, 49%, from **2.99a**); **M.p.**: 141.0 – 142.0 °C; **R_f** = 0.21 (SiO_2, pentane/EtOAc 3:1); **Optical rotation**: $[\alpha]_D^{23}$= +30.5 (*c* 0.93, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3306, 2961, 1690, 1648, 1539, 1448, 1372, 1284, 1253, 1123, 1037, 735, 676 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.77 (d, *J* = 7.7 Hz, 2H), 7.61 – 7.58 (m, 2H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 2H), 5.92 (s, 1H), 4.91 (d, *J* = 9.0 Hz, 1H), 4.41 (d, *J* = 8.5 Hz, 2H), 4.22 (t, *J* = 6.9 Hz, 1H), 3.60 – 3.53 (m, 1H), 3.45 – 3.37 (m, 1H), 3.28 (dt, *J* = 13.7, 4.1 Hz, 1H), 1.93 (s, 3H), 1.84 – 1.76 (m, 1H), 0.97 (d, *J* = 7.3 Hz, 3H), 0.94 (d, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 171.1, 157.5, 144.0, 143.9, 141.5, 127.9, 127.9, 127.2, 125.2, 125.1, 120.1, 120.1, 66.9, 57.0, 47.4, 42.6, 30.9, 23.4, 19.4, 18.3; **HRMS (ESI)** m/z calcd for $C_{22}H_{27}N_2O_3$ $[M+H]^+$: 367.2016, found: 367.2016.

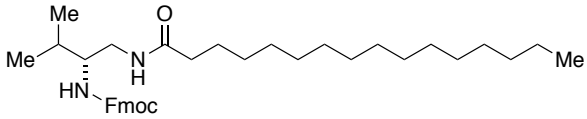
(9*H*-fluoren-9-yl)methyl (*R*)-(1-hexanamido-3-methylbutan-2-yl)-carbamate (2.137a):



White solid (250 mg, 592 *μ*mol, 92%, from **2.99a**); **M.p.:** 128.2 – 128.8 °C; **R_f** = 0.5 (SiO_2, pentane/EtOAc 1:1); **Optical rotation**: $[\alpha]_D^{25}$= +31.3 (*c* = 0.35, $CHCl_3$); **FTIR (neat)**: $\tilde{\nu}$ = 3304, 3070, 2958, 2931, 2872, 2359, 1690, 1542, 1449, 1374, 1251, 1124, 1039, 737, 675 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.77 (d, *J* = 7.5 Hz, 2H), 7.59 (dd, *J* = 7.5, 3.1 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 5.91 (s, 1H), 4.95 (d, *J* = 8.8 Hz,

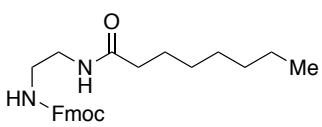
1H), 4.45 – 4.41 (m, 1H), 4.36 – 4.31 (m, 1H), 4.21 (t, *J* = 7.0 Hz, 1H), 3.60 – 3.54 (m, 1H), 3.48 – 3.40 (m, 1H), 3.27 (dt, *J* = 13.6, 3.8 Hz, 1H), 2.12 (t, *J* = 7.7 Hz, 2H), 1.85 – 1.77 (m, 1H), 1.61 – 1.54 (m, 2H), 1.26 – 1.24 (m, 4H), 0.96 (t, *J* = 7.2 Hz, 6H), 0.85 – 0.82 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* = 174.4, 157.5, 144.0, 143.9, 141.5, 127.9, 127.9, 127.2, 125.2, 125.1, 120.1, 120.1, 67.0, 57.1, 47.4, 42.5, 36.8, 31.5, 30.9, 25.5, 22.5, 19.4, 18.4, 14.0; **HRMS (ESI)** m/z calcd for $C_{26}H_{35}N_2O_3$ $[M+H]^+$: 423.2642, found 423.2640.

(9*H*-fluoren-9-yl)methyl (*R*)-(3-methyl 1-palmitamidobutan-2-yl)carbamate (2.137b):



White solid (411.0 mg, 0.73 mmol, 75%, from **2.99a**); **M**.**p**.: 116.5 – 117.3 °C; **R_f** = 0.29 (SiO_2, pentane/EtOAc 2:1); **Optical rotation**: $[\alpha]_D^{25}$ = +23.2 (*c* 0.80, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3392, 3307, 3195, 3069, 2919, 2851, 1691, 1643, 1543, 1468, 1450, 1375, 1287, 1253, 1122, 1035, 736, 653 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* = 7.76 (d, *J* = 7.4 Hz, 2H), 7.58 (dd, *J* = 7.4, 4.0 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 5.91 (bs, 1H), 4.97 (d, *J* = 8.9 Hz, 1H), 4.44 – 4.40 (m, 1H), 4.36 – 4.32 (m, 1H), 4.21 (t, *J* = 7.1 Hz, 1H), 3.60 – 3.53 (m, 1H), 3.49 – 3.41 (m, 1H), 3.28 – 3.22 (m, 1H), 2.11 (t, *J* = 7.8 Hz, 2H), 1.85 – 1.76 (m, 1H), 1.59 – 1.52 (m, 2H), 1.25 – 1.19 (m, 24H), 0.96 (t, *J* = 7.3 Hz, 6H), 0.88 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* = 174.2, 157.5, 144.0, 144.0, 141.5, 127.9, 127.9, 127.2, 125.2, 125.2, 120.1, 120.1, 67.0, 57.1, 47.4, 42.4, 37.0, 36.0, 32.1, 30.9, 29.9, 29.8, 29.8, 29.8, 29.8, 29.6, 29.5, 29.5, 29.5, 29.4, 25.9, 25.7, 22.8, 19.4, 18.3, 14.3; **HRMS (ESI)** m/z calcd for $C_{36}H_{55}N_2O_3$ $[M+H]^+$: 563.4207, found: 563.4207.

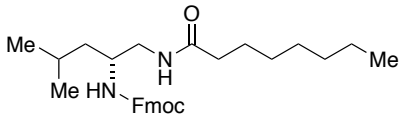
(9*H*-fluoren-9-yl)methyl (2-octanamidoethyl)carbamate (2.133d):



White solid (1.86 g, 4.56 mmol, 68%, from **2.132d**); **M**.**p**.: 154.3 – 154.6 °C (decomposition); **R_f** = 0.18 (SiO_2, pentane/EtOAc 1:1; **FTIR (neat):** $\tilde{\nu}$ = 3331, 2949, 2925, 2854, 1691, 1649, 1538, 1448, 1379, 1268, 1234, 1157, 995, 736, 646 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* = 7.76 (d, *J* = 7.5 Hz, 2H), 7.58 (d, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 6.10 (s,

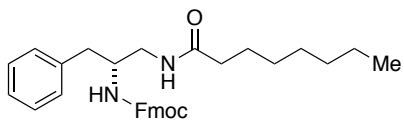
1H), 5.36 (s, 1H), 4.39 (d, *J* = 7.0 Hz, 2H), 4.20 (t, *J* = 7.0 Hz, 1H), 3.39 – 3.32 (m, 4H), 2.19 – 2.14 (m, 2H), 1.62 – 1.58 (m, 2H), 1.29 – 1.23 (m, 8H), 0.87 – 0.84 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* = 174.3, 157.4, 144.0, 141.4, 127.9, 127.2, 125.2, 120.1, 67.0, 47.3, 41.2, 40.3, 36.8, 31.8, 31.8, 29.4, 29.1, 25.8, 22.7, 14.2; **HRMS (ESI)** m/z calcd for $C_{25}H_{33}N_2O_3$ $[M+H]^+$: 409.2486, found: 409.2485.

(9*H*-fluoren-9-yl)methyl (*R*)-(4-methyl-1-octanamidopentan-2-yl)-carbamate (2.133b):



White solid (2.33 g, 5.02 mmol, 46%, from **2.132b**); rotameric compound; **M**.**p**.: 136.8 – 137.4 °C; **R_f** = 0.15 (SiO_2, pentane/EtOAc 3:1); **Optical rotation**: $[\alpha]_D^{25}$ = +21.3 (*c* 1.11, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3428, 3302, 2955, 2926, 2854, 1682, 1647, 1538, 1450, 1316, 1272, 1234, 1121, 1084, 1021, 951, 734 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* = 7.76 (d, *J* = 7.6 Hz, 2H), 7.58 (dd, *J* = 7.5, 5.0 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.35 – 7.28 (m, 5H), 7.26 – 7.23 (m, 2H), 7.20 – 7.15 (m, 1H), 6.29 (bs, 1H), 5.01 (d, *J* = 8.5 Hz, 1H), 4.44 – 4.33 (m, 2H), 4.20 (t, *J* = 6.9 Hz, 1H), 3.79 (bs, 1H), 3.46 (bs, 1H), 3.39 – 3.31 (m, 1H), 3.25 – 3.21 (m, 1H), 2.13 (t, *J* = 7.6 Hz, 2H), 1.69 – 1.62 (m, 1H), 1.59 – 1.52 (m, 2H), 1.40 – 1.33 (m, 1H), 1.28 – 1.21 (m, 8H), 0.91 (t, *J* = 6.4 Hz, 6H), 0.83 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* = 174.4, 157.2, 150.9, 150.8, 143.9, 143.9, 141.4, 141.4, 129.9, 127.9, 127.2, 127.2, 125.3, 125.3, 125.2, 125.1, 120.5, 120.4, 120.1, 120.1, 66.9, 50.0, 47.4, 45.0, 42.1, 36.7, 31.8, 29.4, 29.1, 25.9, 24.9, 23.1, 22.7, 22.2, 14.2; **HRMS (ESI)** m/z calcd for $C_{29}H_{40}N_2O_3Na$ $[M+Na]^+$: 487.2931, found: 487.2926.

(9*H*-fluoren-9-yl)methyl (*R*)-(1-octanamido-3-phenylpropan-2-yl)-carbamate (2.133c):



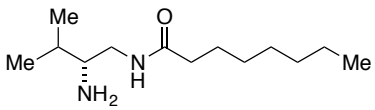
Yellow solid (1.56 g, 3.12 mmol, 57%, from **2.132c**); **M**.**p**.: 160.1 – 160.7 °C; **R_f** = 0.49 (SiO_2, pentane/EtOAc 1:1); **Optical rotation**: $[\alpha]_D^{25}$= +22.8 (*c* 0.42, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3308, 3064, 2925, 2854, 1690,

1642, 1543, 1446, 1316, 1265, 1148, 1085, 1061, 1036, 736, 698 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 7.5 Hz, 2H), 7.54 (d, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 4H), 7.23 – 7.19 (m, 3H), 5.87 (bs, 1H), 5.27 (d, *J* = 7.9 Hz, 1H), 4.41 – 4.27 (m, 2H), 4.18 (t, *J* = 7.0 Hz, 1H), 3.96 (bs, 1H), 3.49 – 3.28 (m, 2H), 2.93 – 2.76 (m, 2H), 2.17 – 2.12 (m, 2H), 1.62 – 1.52 (m, 2H), 1.28 – 1.22 (m, 8H), 0.84 (t, *J* = 6.8, Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 174.5, 156.8, 144.0, 144.0, 141.4, 137.7, 129.3, 128.8, 127.8, 127.2, 126.9, 125.3, 125.2, 120.1, 67.0, 53.5, 47.3, 43.4, 39.2, 36.8, 31.8, 29.4, 29.1, 25.9, 22.7, 14.2; **HRMS (ESI)** m/z calcd for $C_{32}H_{39}N_2O_3$ $[M+H]^+$: 499.2955, found: 499.2955.

General procedure for the Fmoc-deprotection:

The Fmoc-protected amine (1.86 mmol, 1.0 eq) was dissolved in dry toluene (36 mL) and $AlCl_3$ (5.59 mmol, 3.0 eq) was added at r.t. The yellow solution turned to dark violet over 4 h. Aq. HCl (1 M, 20 mL) was added (pH = 1) and the aq. layer extracted with Et_2O (3 x 15 mL). Sat. $NaHCO_3$ (45 mL) was added carefully added to the acidic layer. The basic aq. layer (pH = 8) was extracted with CH_2Cl_2 (5 x 15 mL). The combined organic layer was washed with brine (10 mL) and the organic layer was dried over Na_2SO_4, filtered and evaporated to obtain the desired free amine as a colorless oil.

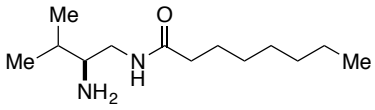
(*R*)-*N*-(2-amino-3-methylbutyl)octanamide (2.101a):



Colorless oil (403 mg, 1.77 mmol, 95%, from **2.100a**); **R_f** = 0.13 (SiO_2, CH_2Cl_2/MeOH 1:1); **Optical rotation**: $[\alpha]_D^{25}$ = –34.4 (*c* 0.90, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3291, 3074, 2956, 2926, 2868, 1642, 1548, 1464, 1369, 1268, 1119, 1029, 671, 629 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.16 (bs, 1H) 3.54 – 3.48 (m, 1H), 2.92 – 2.86 (m, 1H), 2.58 – 2.54 (m, 1H), 2.18 (t, *J* = 7.5 Hz, 2H), 1.66 – 1.56 (m, 5H), 1.31 – 1.23 (m, 8H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.86 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 173.5, 56.8, 43.1, 37.0, 32.6, 31.8, 29.4, 29.2, 26.0, 22.7, 19.3, 17.9, 14.2; **HRMS (ESI)** m/z calcd for $C_{13}H_{28}N_2O$ $[M+H]^+$: 229.2274, found:

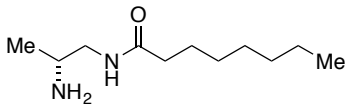
229.2274.

(*S*)-*N*-(2-amino-3-methylbutyl)octanamide (2.101b):



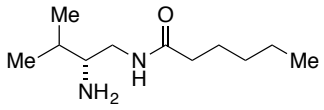
Colorless oil (330 mg, 1.45 mmol, 92% from **2.100b**); **Optical rotation**: $[\alpha]_D^{25}$= +41.7 (*c* 0.32, $CHCl_3$).

(9*H*-fluoren-9-yl)methyl (*R*)-(1-octanamidopropan-2-yl)carbamate (2.134a):



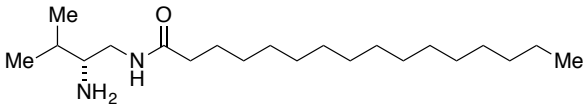
Colorless oil (545 mg, 2.72 mmol, 96%, from **2.134a**); $\mathbf{R_f}$ = 0.33 (SiO_2, CH_2Cl_2/MeOH 1:1); **Optical rotation**: $[\alpha]_D^{25}$ = –21.2 (*c* 0.57, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3281, 3073, 2957, 2925, 2857, 1643, 1544, 1460, 1361, 1269, 1240, 1116, 1033, 963, 831, 698 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* = 6.16 (bs, 1H), 3.31 – 3.26 (m, 1H), 3.06 – 2.93 (m, 2H), 2.16 (t, *J* = 7.9 Hz, 2H), 1.64 – 1.58 (m, 4H), 1.30 – 1.21 (m, 8H), 1.06 (d, *J* = 6.2 Hz, 3H), 0.84 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* = 173.6, 46.9, 46.7, 37.0, 31.8, 29.4, 29.1, 26.0, 22.7, 21.9, 14.2; **HRMS (ESI)** m/z calcd for $C_{11}H_{25}N_2O$ $[M+H]^+$: 201.1961, found: 201.1963.

(*R*)-*N*-(2-amino-3-methylbutyl)hexanamide (2.138a):



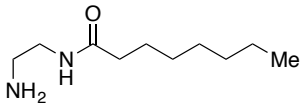
Colorless oil (57.0 mg, 285 *μ*mol, 80%, from **2.137a**); $\mathbf{R_f}$ = 0.12 (SiO_2, CH_2Cl_2/MeOH 1:1); **Optical rotation:** $[\alpha]_D^{23}$ = –37.3 (*c* 0.16, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3293, 3074, 2957, 2930, 2871, 2340, 1643, 1548, 1465, 1370, 1255, 1188, 1115, 631 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) *δ* = 6.31 (s, 1H), 3.43 (ddd, *J* = 13.4, 6.5, 3.8 Hz, 1H), 2.84 (ddd, *J* = 13.5, 9.2, 4.3 Hz, 1H), 2.50 (ddd, *J* = 9.4, 5.6, 3.8 Hz, 1H), 2.15 – 2.11 (m, 2H), 1.61 – 1.50 (m, 3H), 1.39 (s, 2H), 1.29 – 1.21 (m, 4H), 0.88 – 0.81 (m, 9H); **^{13}C NMR** ($CDCl_3$, 101 MHz) *δ* = 173.5, 56.6, 43.3, 36.8, 32.5, 31.5, 25.6, 22.4, 19.3, 17.7, 14.0; **HRMS (ESI)** m/z calcd for $C_{11}H_{25}N_2O$ $[M+H]^+$: 201.1961, found 201.1964.

(*R*)-*N*-(2-amino-3-methylbutyl)palmitamide (2.138b):



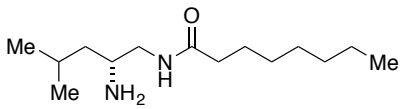
White solid (3.81 mg, 11.0 μmol, 45%, from **2.137b**); **M.p.**: 55.8 – 57.5 °C; $\mathbf{R_f}$ = 0.41 (SiO_2, CH_2Cl_2/MeOH 1:1); **Optical rotation**: $[\alpha]_D^{25}$ = –16.5 (*c* 0.18, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3309, 2957, 2916, 2850, 1635, 1548, 1469, 1381, 1262, 1089, 1018, 800, 718 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.05 (bs, 1H), 3.54 – 3.48 (m, 1H), 2.91 – 2.84 (m, 1H), 2.56 – 2.52 (m, 1H), 2.18 (t, *J* = 7.8 Hz, 2H), 1.66 – 1.54 (m, 3H), 1.30 – 1.25 (m, 26H), 0.92 (t, *J* = 6.6 Hz, 6H), 0.88 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 173.5, 56.7, 43.3, 37.1, 32.8 32.1, 29.9, 29.8, 29.8, 29.7, 29.7, 29.5, 29.5, 29.5, 26.0, 22.9, 19.4, 17.9, 14.3; **HRMS (ESI)** m/z calcd for $C_{21}H_{45}N_2O$ $[M+H]^+$: 341.3526, found: 341.3528.

***N*-(2-aminoethyl)octanamide (2.134d):**



White solid (380 mg, 2.04 mmol, 69%, from **2.133d**); **M.p.**: 117.8 – 118.6 °C; $\mathbf{R_f}$ = 0.28 (SiO_2, CH_2Cl_2/MeOH 1:1); **FTIR (neat):** $\tilde{\nu}$ = 3287, 2955, 2921, 2853, 1637, 1551, 1466, 1380, 1286, 1210, 1121, 1042, 927, 694 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.10 (s, 1H), 3.29 (q, *J* = 5.8 Hz, 2H), 2.82 (t, *J* = 5.9 Hz, 2H), 2.17 (t, *J* = 7.6 Hz, 2H), 1.73 (s, 2H), 1.61 (quin., *J* = 7.4 Hz, 2H), 1.30 – 1.23 (m, 8H), 0.87 – 0.84 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 173.7, 41.9, 41.5, 37.0, 31.8, 29.4, 29.1, 25.9, 22.7, 14.2; **HRMS (ESI)** m/z calcd for $C_{10}H_{23}N_2O$ $[M+H]^+$: 187.1805, found: 187.1805.

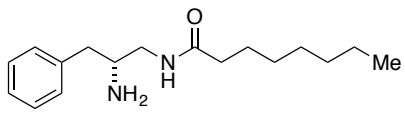
(*R*)-*N*-(2-amino-4-methylpentyl)octanamide (2.134b):



White solid (200 mg, 0.825 mmol, 54%, from **2.133b**); **M.p.**: 83.9 – 84.6 °C; $\mathbf{R_f}$ = 0.46 (SiO_2, CH_2Cl_2/MeOH 1:1); **Optical rotation**: $[\alpha]_D^{25}$ = –11.9 (*c* 0.34, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3303, 2955, 2920, 2852, 1645, 1557, 1486, 1368, 1331, 1284, 1168, 1144, 1067, 816, 716, 636 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.23 (bs, 1H), 3.44 – 3.41 (m, 1H), 3.01 – 2.95 (m, 2H), 2.30 (bs, 2H), 2.19 (t, *J* = 7.8 Hz, 2H), 1.76 – 1.68 (m, 1H), 1.65 – 1.59 (m, 2H), 1.32 – 1.22 (m, 10H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.88 (t, *J* = 6.5 Hz, 3H), 0.87 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 173.8, 49.3, 45.1, 44.7, 37.0,

31.8, 29.4, 29.2, 25.9, 24.7, 23.3, 22.8, 22.3, 14.2; **HRMS (ESI)** m/z calcd for $C_{14}H_{31}N_2O$ $[M+H]^+$: 243.2431, found: 243.2434.

(*R*)-*N*-(2-amino-3-phenylpropyl)octanamide (2.134c):

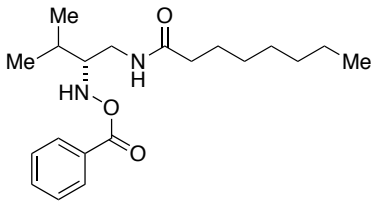


Slightly yellow oil (8.0 mg, 0.029 mmol, 87%, from **2.133c**); $\mathbf{R_f}$ = 0.50 (SiO_2, CH_2Cl_2/MeOH 1:1); **Optical rotation**: $[\alpha]_D^{25}$ = –6.3 (*c* 0.27, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3281, 3062, 2925, 2855, 1643, 1546, 1455, 1377, 1265, 1086, 1030, 889, 799, 743, 702, 630 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.32 – 7.29 (m, 2H), 7.25 – 7.18 (m, 3H), 6.15 (t, *J* = 5.3 Hz, 1H), 3.52 – 3.46 (m, 1H), 3.22 – 3.16 (m, 1H), 3.14 – 3.08 (m, 1H), 2.84 (dd, *J* = 13.4, 5.2 Hz, 1H), 2.58 (dd, *J* = 13.4, 8.2 Hz, 1H), 2.28 (bs, 2H), 2.19 (t, *J* = 7.5, Hz, 2H), 1.65 – 1.58 (m, 2H), 1.31 – 1.25 (m, 8H), 0.88 – 0.85 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 173.8, 138.1, 129.4, 128.8, 126.8, 52.8, 44.7, 42.0, 37.0, 31.9, 29.5, 29.2, 25.9, 22.8, 14.2; **HRMS (ESI)** m/z calcd for $C_{17}H_{29}N_2O$ $[M+H]^+$: 277.2274, found: 277.2278.

General procedure for the *N*-oxidation:

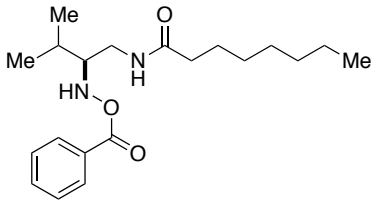
Dibenzoylperoxide (0.44 mmol, 1.3 eq) and K_2HPO_4 (0.55 mmol, 1.6 eq) were suspended in THF (2.1 mL). The free amine (0.34 mmol, 1.2 eq) was dissolved in THF (0.9 mL) and added to the mixture and stirred for 21.5 h at r.t. Eight drops of piperidine were added and the mixture stirred for 10 minutes. Water (5.0 mL) was added and stirring continued at r.t. until a solution was obtained. The solution was extracted with EtOAc (3 x 1.2 mL) and the combined organic layers were washed with brine (2 x 1.0 mL), then dried over Na_2SO_4, filtered and evaporated to obtain a yellow oil. The crude was purified by flash column chromatography (SiO_2, pentane/EtOAc 3:1) to obtain the desired *N*-oxide product.

(*R*)-*N*-(2-((benzoyloxy)amino)-3-methylbutyl)octanamide (2.102a):



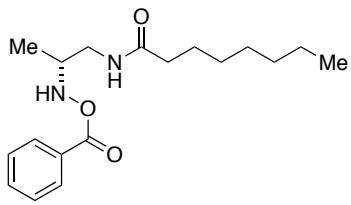
Colorless oil (298 mg, 0.89 mmol, 56%, from **2.101a**); $\mathbf{R_f}$ = 0.27 (SiO_2, pentane/EtOAc 3:1); **Optical rotation**: $[\alpha]_D^{25}$ = –1.2 (*c* 0.18, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3289, 3066, 2967, 2927, 2857, 1724, 1643, 1544, 1491, 1452, 1380, 1335, 1263, 1178, 1090, 1025, 982, 858, 786, 707 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.01 – 7.98 (m, 2H), 7.64 – 7.59 (m, 2H), 7.50 – 7.45 (m, 2H), 6.38 (bs, 1H), 3.73 – 3.65 (m, 1H), 3.33 – 3.26 (m, 1H), 2.98 – 2.93 (m, 1H), 2.25 – 2.21 (m, 2H), 1.90 (m, *J* = 6.7 Hz, 1H), 1.68 – 1.60 (m, 2H), 1.30 – 1.23 (m, 8H), 1.10 (d, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 173.6, 167.0, 133.8, 129.5, 128.8, 128.2, 66.7, 38.3, 37.0, 31.8, 29.4, 29.2, 28.3, 25.9, 22.8, 19.5, 19.4, 14.2; **HRMS (ESI)** m/z calcd for $C_{20}H_{32}N_2O_3$ $[M+H]^+$: 349.2486, found: 349.2490.

(*S*)-*N*-(2-((benzoyloxy)amino)-3-methylbutyl)octanamide (2.102b):



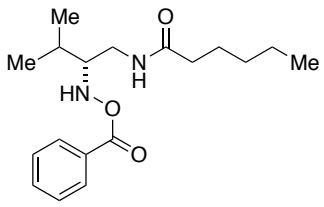
Colorless oil (81.8 mg, 0.235 mmol, 69% from **2.101b)**; **Optical rotation**: $[\alpha]_D^{25}$ = +0.7 (*c* 0.17, $CHCl_3$).

(*R*)-*N*-(2-((benzoyloxy)amino)propyl) octanamide (2.135a):



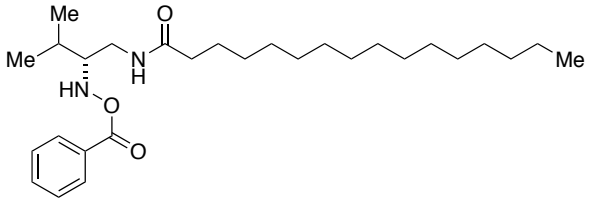
Colorless oil (137 mg, 0.427 mmol, 16%, from **2.134b**); $\mathbf{R_f}$ = 0.39 (SiO_2, pentane/EtOAc 1:1); **Optical rotation**: $[\alpha]_D^{25}$ = +5.7 (*c* 0.10, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3305, 2954, 2927, 2856, 1722, 1647, 1543, 1452, 1264, 1177, 1087, 1063, 1025, 797, 707 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.03 – 8.00 (m, 2H), 7.63 – 7.59 (m, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 6.12 (bs, 1H), 3.51 – 3.45 (m, 1H), 3.42 – 3.30 (m, 2H), 2.22 (t, *J* = 7.7 Hz, 2H), 1.68 – 1.61 (m, 2H), 1.36 – 1.26 (m, 8H), 1.19 (d, *J* = 6.3 Hz, 3H), 0.87 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 173.7, 167.2, 133.8, 129.5, 128.8, 128.1, 56.5, 41.5, 37.0, 31.8, 29.4, 29.2, 25.9, 22.8, 15.7, 14.2; **HRMS (ESI)** m/z calcd for $C_{18}H_{29}N_2O_3$ $[M+H]^+$: 321.2173, found: 321.2174.

(*R*)-*N*-(2-((benzoyloxy)amino)-3-methylbutyl)hexanamide (2.139a):



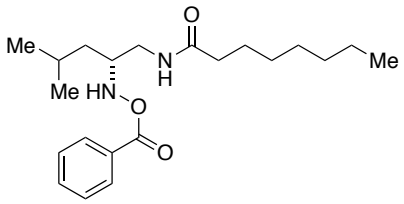
Colorless oil (7.41 mg, 23.1 *µ*mol, 77%, from **2.138a**); $\mathbf{R_f}$ = 0.28 (SiO_2, pentane/EtOAc 3:1); **Optical rotation**: $[\alpha]_D^{25}$ = –10.3 (*c* 0.18, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3297, 3067, 2957, 2931, 2870, 2361, 1721, 1643, 1543, 1450, 1370, 1268, 1178, 1090, 1066, 1025, 853, 794, 708, 656, 627 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) *δ* = 7.99 (d, *J* = 6.9 Hz, 2H), 7.63 – 7.59 (m, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 6.36 (s, 1H), 3.69 (ddd, *J* = 14.2, 6.0, 3.5 Hz, 1H), 3.28 (ddd, *J* = 13.8, 8.1, 5.0 Hz, 1H), 2.94 (td, *J* = 7.7, 3.5 Hz, 1H), 2.22 (t, *J* = 7.6 Hz, 2H), 1.98 – 1.89 (m, 1H), 1.68 – 1.61 (m, 3H), 1.35 – 1.25 (m, 4H), 1.10 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.90 – 0.87 (m, 3H); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ = 173.8, 166.8, 133.9, 129.6, 128.8, 66.8, 38.2, 36.9, 31.6, 28.3, 25.5, 24.8, 22.6, 19.6, 19.3, 14.1; **HRMS (ESI)** m/z calcd for $C_{18}H_{29}N_2O_3$ $[M+H]^+$: 321.2173, found 321.2173.

(*R*)-*N*-(2-((benzoyloxy)amino)-3-methylbutyl)palmitamide (2.139b):



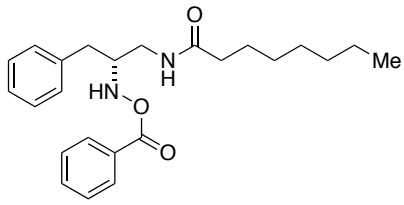
Colorless oil (4.7 mg, 0.01 mmol, 43%, from **2.138b**); $\mathbf{R_f}$ = 0.27 (SiO_2, pentane/EtOAc 3:1); **Optical rotation**: $[\alpha]_D^{25}$ = –1.2 (*c* 0.41, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3314, 2916, 2852, 1720, 1640, 1549, 1469, 1450, 1428, 1270, 1179, 1107, 1097, 1068, 1026, 794, 702, 687 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* = 8.01 – 7.98 (m, 2H), 7.88 (bs, 1H), 7.62 – 7.57 (m, 1H), 7.48 – 7.44 (m, 2H), 6.23, (t, *J* = 5.6 Hz, 1H), 3.69 – 3.63 (m, 1H), 3.28 – 3.21 (m, 1H), 2.89 – 2.85 (m, 1H), 2.20 (t, *J* = 7.9 Hz, 2H), 1.95 – 1.83 (m, 1H), 1.67 – 1.59 (m, 2H), 1.28 – 1.24 (m, 24H), 1.08 (d, *J* = 6.7 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.87 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* = 173.6, 167.1, 133.7, 129.5, 128.8, 128.5, 128.2, 126.9, 66.6, 38.3, 37.0, 32.1, 29.8, 29.8, 29.8, 29.7, 29.5, 29.5, 28.3, 25.6, 22.8, 19.5, 19.4, 14.3; **HRMS (ESI)** m/z calcd for $C_{28}H_{49}N_2O_3$ $[M+H]^+$: 461.3738, found: 461.3741.

(*R*)-*N*-(2-((benzoyloxy)amino)-4-methylpentyl)octanamide (2.135b):



Colorless oil (111 mg, 0.306 mmol, 42%, from **2.134b**); $\mathbf{R_f}$ = 0.23 (SiO_2, pentane/EtOAc 5:1); **Optical rotation**: $[\alpha]_D^{25}$ = +6.4 (*c* 0.35, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3301, 3065, 2928, 2857, 1721, 1640, 1620, 1544, 1449, 1369, 1269, 1176, 1091, 1025, 852, 789, 707 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.01 – 7.98 (m, 2H), 7.60 (t, *J* = 7.5, 1.3 Hz, 1H), 7.49 – 7.45 (m, 2H), 6.27 (bs, 1H), 3.53 – 3.47 (m, 1H), 3.36 – 3.26 (m, 2H), 2.21 (t, *J* = 7.7 Hz, 2H), 1.85 – 1.75 (m, 1H), 1.68 – 1.60 (m, 3H), 1.46 – 1.36 (m, 1H), 1.35 – 1.24 (m, 9H), 0.94 (d, *J* = 6.6 Hz, 6H), 0.86 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 173.6, 167.1, 133.7, 129.5, 128.8, 128.5, 126.9, 59.0, 40.4, 38.6, 37.0, 31.8, 29.4, 29.1, 25.9, 24.9, 23.0, 22.7, 14.2; **HRMS (ESI)** m/z calcd for $C_{21}H_{35}N_2O_3$ $[M+H]^+$: 363.2642, found: 363.2642.

(*R*)-*N*-(2-((benzoyloxy)amino)-3-phenylpropyl)octanamide (2.135c):

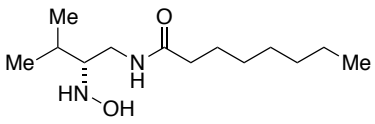


Colorless oil (88.1 mg, 0.22 mmol, 46%, from **2.134c**); $\mathbf{R_f}$ = 0.20 (SiO_2, pentane/EtOAc 3:1); **Optical rotation**: $[\alpha]_D^{25}$ = +19.1 (*c* 0.24, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3296, 2927, 2856, 1722, 1646, 1519, 1453, 1360, 1251, 1162, 1064, 1026, 800, 704 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.91 (d, *J* = 7.6 Hz, 2H) 7.55 (t, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.32 – 7.25 (m, 3H), 7.21 – 7.17 (m, 2H), 6.32 (bt, *J* = 5.4 Hz, 1H), 3.58 – 3.53 (m, 1H), 3.43 – 3.39 (m, 1H), 3.36 – 3.30 (m, 1H), 2.82 (d, *J* = 6.9 Hz, 2H), 2.17 (t, *J* = 7.8 Hz, 2H), 1.62 – 1.47 (m, 3H), 1.26 – 1.19 (m, 8H), 0.82 – 0.78 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 173.7, 166.8, 137.2, 133.7, 129.5, 129.3, 129.0, 128.8, 128.2, 127.1, 62.3, 40.2, 37.0, 36.4, 31.8, 29.4, 29.1, 25.9, 22.7, 14.2; **HRMS (ESI)** m/z calcd for $C_{24}H_{33}N_2O_3$ $[M+H]^+$: 397.2486, found: 397.2488.

General procedure for the benzoyl-cleavage:

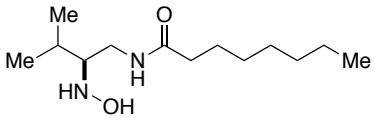
The *N*-oxidized product (23.4 μmol, 1 eq) was dissolved in dry and degassed EtOH (0.5 mL, thaw/freeze method, 3 cycles) and hydrazine monohydrate (0.91 mmol, 39.0 eq) was added and the mixture stirred at r.t. for 2.5 h. The mixture was evaporated and then suspended in ACN. The suspension was filtered over cotton and then evaporated. The filtrate was dissolved in Et_2O (1.5 mL) and aq. HCl (0.25 M, 0.5 mL) and the aq. layer was extracted with Et_2O (3 x 1.0 mL). To the acidic aq. layer was added aq. NaOH solution (10 N) until a basic pH was reached. The basic layer was extracted with Et_2O (4 x 1.5 mL) and the combined organic layers were dried over Na_2SO_4, filtered and evaporated to obtain the desired hydroxylamine as a white solid.

(*R*)-*N*-(2-(hydroxyamino)-3-methylbutyl)octanamide (2.91a):



White solid (36.0 mg, 0.147 mmol, 53%, from **2.102a**); **M.p.**: 107.1 – 107.7 °C; $\mathbf{R_f}$ = 0.16 (SiO_2, pentane/EtOAc 1:1); **Optical rotation**: $[\alpha]_D^{25}$ = –12.3 (*c* 0.26, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3311, 3264, 3194, 2950, 2920, 2860, 2852, 1633, 1561, 1466, 1374, 1244, 1163, 1116, 1067, 1003, 912, 832, 721, 671 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.10 (bs, 1H), 5.34 (bs, 2H), 3.63 – 3.57 (m, 1H), 3.33 – 3.26 (m, 1H), 2.54 (dt, *J* = 7.7, 3.3 Hz, 1H), 2.19 (t, *J* = 7.6 Hz, 2H), 1.86 – 1.74 (m, 1H), 1.65 – 1.59 (m, 2H), 1.29 – 1.25 (m, 8H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.88 – 0.85 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 175.0, 67.2, 38.2, 37.0, 31.8, 29.4, 29.2, 27.5, 25.9, 22.8, 19.7, 19.5, 14.2; **HRMS (ESI)** m/z calcd for $C_{13}H_{29}N_2O_2$ $[M+H]^+$: 245.2224, found: 245.2226.

(*S*)-*N*-(2-(hydroxyamino)-3-methylbutyl)octanamide (2.91b):

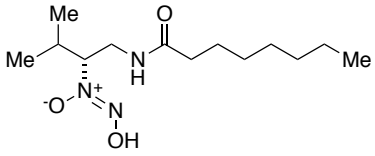


White solid (3.21 mg, 13.2 μmol, 56% from **2.102b)**; **Optical rotation**: $[\alpha]_D^{25}$ = +12.5 (*c* 0.16, $CHCl_3$).

General procedure for the formation *of C*-diazeniumdiolates:

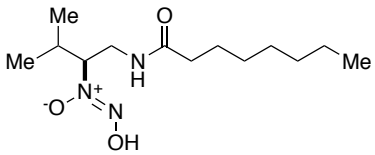
The hydroxylamine (0.14 mmol, 1.0 eq) was dissolved in degassed EtOH (1.4 mL, thaw/freeze method, 3 cycles), isopentyl nitrite (0.97 mmol, 7.0 eq) was added and NH_3 gas was bubbled through the solution for two minutes and after 10 minutes again for one minute. After stirring 30 minutes at r.t., the mixture was evaporated and then extracted with aq. NaOH (1.0 M, 0.4 mL) and Et_2O (4 x 1.0 mL). The basic aq. layer was then acidified with aq. HCl (1.0 M 0.5 mL,) and extracted with Et_2O (4 x 1.2 mL). The combined organic layer was washed with brine (1 mL), dried over Na_2SO_4, filtered and evaporated to obtain the *C*-diazeniumdiolate as a white solid

(*R,Z*)-2-hydroxy-1-(3-methyl-1-octanamidobutan-2-yl)diazene 1-oxide (2.80a):



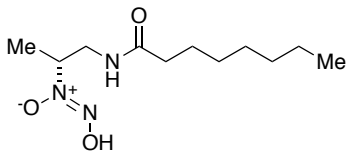
White solid (31.4 mg, 0.12 mmol, 83%, from **2.91a**); **M.p.**: 75.2 – 75.9 °C; $\mathbf{R_f}$ = 0.32 (SiO_2, CH_2Cl_2/MeOH 20:1); **Optical rotation**: $[\alpha]_D^{25}$ = –97.7 (*c* 0.54, $CHCl_3$); –134.2 (*c* 0.53, EtOH); **FTIR (neat):** $\tilde{\nu}$ = 3300, 2961, 2926, 2857, 1622, 1566, 1521, 1466, 1424, 1269, 1058, 931, 707 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 11.75 (bs, 1H), 5.73 (bs, 1H), 4.20 (td, *J* = 9.2, 3.0 Hz, 1H), 3.85 (dq, *J* = 14.2, 3.1 Hz, 1H), 3.63 – 3.56 (m, 1H), 2.27 – 2.12 (m, 3 H), 1.61 – 1.54 (m, 2H), 1.33 – 1.22 (m, 8H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.87 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 173.7, 78.0, 39.1, 36.6, 31.8, 29.3, 29.1, 29.1, 25.7, 22.7, 19.1, 18.9, 14.2; **HRMS (ESI)** m/z calcd for $C_{13}H_{27}N_3O_3Na$ $[M+Na]^+$: 296.1945, found: 296.1945; **X-ray crystal structure** is given in the appendices section.

(*S,Z*)-2-hydroxy-1-(3-methyl-1-octanamidobutan-2-yl)diazene 1-oxide (2.80b):



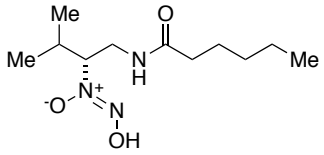
White solid (9.46 mg, 35 μmol, 83% from **2.91b**); **Optical rotation**: $[\alpha]_D^{25}$ = +126.2 (*c* 0.50, $CHCl_3$); $[\alpha]_D^{25}$ = +147.0 (*c* 0.47, EtOH).

(*R*,*Z*)-2-hydroxy-1-(1-octanamidopropan-2-yl)diazene 1-oxide (2.136a):



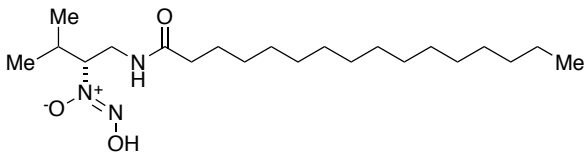
White solid (12.9 mg, 53.0 μmol, 65%, over two steps from **2.135a**); **M**.**p**.: 48.3 – 48.7 °C; $\mathbf{R_f}$ = 0.08 (SiO_2, CH_2Cl_2/MeOH 20:1); **Optical rotation**: $[\alpha]_D^{25}$ = –110 (*c* 0.30, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3310, 2954, 2927, 2848, 1650, 1547, 1446, 1380, 1332, 1285, 1266, 1250, 1109, 1046, 946, 689, 667, 637 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 11.53 (bs, 1H), 5.85 (t, *J* = 6.3 Hz, 1H), 4.70 – 4.59 (m, 1H), 3.74 (ddd, *J* = 14.5, 6.4, 3.3 Hz, 1H), 3.56 – 3.46 (m, 1H), 2.18 – 2.13 (m, 2H), 1.58 (quin., *J* = 7.1 Hz, 2H), 1.48 (d, *J* = 6.8 Hz, 3H), 1.30 – 1.24 (m, 8H), 0.89 – 0.84 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 173.9, 68.1, 41.8, 36.6, 31.8, 29.3, 29.1, 25.8, 22.7, 15.9, 14.2; **HRMS (ESI)** m/z calcd for $C_{11}H_{23}N_3O_3Na$ $[M+Na]^+$: 268.16316, found: 268.16291.

(*R*,*Z*)-1-(1-hexanamido-3-methylbutan-2-yl)-2-hydroxydiazene 1-oxide (2.140a):



White solid (6.46 mg, 17.8 *μ*mol, 31% over two steps from **2.139a**); **M.p.:** 51.5 – 52.7 °C; $\mathbf{R_f}$ = 0.14 (SiO_2, CH_2Cl_2/MeOH 20:1); **Optical rotation:** $[\alpha]_D^{26}$= –88.2 (*c* 0.08, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3294, 2962, 2929, 2862, 2362, 1621, 1529, 1459, 1425, 1268, 1057, 930, 876, 800, 710 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ = 11.60 (s, 1H), 5.71 (s, 1H), 4.21 (td, *J* = 9.2, 3.1 Hz, 1H), 3.86 (ddd, *J* = 14.4, 6.0, 3.1 Hz, 1H), 3.60 (ddd, *J* = 14.3, 9.4, 6.0 Hz, 1H), 2.25 – 2.11 (m, 3H), 1.62 – 1.55 (m, 2H), 1.34 – 1.25 (m, 4H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.91 – 0.87 (m, 6H); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ = 173.7, 78.0, 39.1, 36.6, 31.4, 29.1, 25.4, 22.5, 19.2, 18.9, 14.0; **HRMS (ESI)** m/z calcd for $C_{11}H_{23}N_3NaO_3$ $[M+Na]^+$: 268.1632, found 268.1633; **X-ray crystal structure** is given in the appendices section.

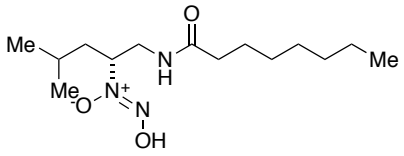
(*R*,*Z*)-2-hydroxy-1-(3-methyl-1-palmitamidobutan-2-yl)diazene 1-oxide (2.140b):



White solid (3.02 mg, 8.0 μmol, 52%, over two steps from **2.139b**); **M**.**p**.: 93.5 – 93.9 °C $\mathbf{R_f}$ = 0.08

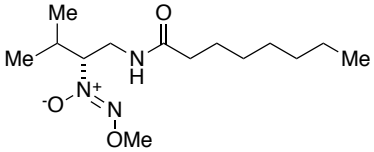
(SiO_2, CH_2Cl_2/MeOH 20:1); **Optical rotation**: $[\alpha]_D^{25}$ = –70.7 (*c* 0.27, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3325, 2915, 2847, 1651, 1544, 1472, 1462, 1250, 1055, 730, 714, 685, 619 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 11.69 (s, 1H), 5.70 (t, *J* = 5.5 Hz, 1H), 4.20 (td, *J* = 9.2, 3.1 Hz, 1H), 3.89 – 3.83 (m, 1H), 3.64 – 3.56 (m, 1H), 2.25 – 2.18 (m, 1H), 2.16 – 2.12 (m, 2H), 1.61 – 1.54 (m, 2H), 1.32 – 1.21 (m, 24H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.90 – 0.86 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 173.7, 78.0, 39.1, 36.7, 32.1, 29.9, 29.9, 29.8, 29.8, 29.8, 29.8, 29.6, 29.5, 29.5, 29.3, 29.1, 25.8, 22.9, 19.2, 18.9, 14.3; **HRMS (ESI)** m/z calcd for $C_{21}H_{43}N_3O_3Na$ $[M+Na]^+$: 408.31966, found: 408.31932.

(*R*,*Z*)-2-hydroxy-1-(4-methyl-1-octanamidopentan-2-yl)diazene 1-oxide (2.136b):



White solid (17.8 mg, 62.0 μmol, 38% over two steps from **2.135b**); **M.p.**: 74.0 – 74.4 °C; **R_f** = 0.15 (SiO_2, CH_2Cl_2/MeOH 20:1); **Optical rotation**: $[\alpha]_D^{25}$ = –72.1 (*c* 0.25, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3316, 2953, 2927, 2656, 2360, 1623, 1566, 1523, 1455, 1424, 1360, 1326, 1271, 1222, 1173, 1143, 1088, 1062, 1030, 1007, 947, 696, 615, cm^{-1}; **^{1}H NMR** (400 MHz, MeOD) δ = 4.60 – 4.53 (m, 1H), 3.53 – 3.39 (m, 2H), 2.15 (t, *J* = 7.6 Hz, 2H), 1.92 – 1.85 (m, 1H), 1.61 – 1.53 (m, 2H), 1.51 – 1.37 (m, 2H), 1.33 – 1.27 (m, 8H), 0.95 – 0.88 (m, 9H); **^{13}C NMR** (101 MHz, MeOD) δ = 177.0, 71.7, 42.5, 39.4, 36.9, 32.8, 30.2, 30.1, 27.0, 26.0, 23.7, 23.3, 21.7, 14.4; **HRMS (ESI)** m/z calcd for $C_{14}H_{29}N_3O_3Na$ $[M+Na]^+$: 310.21011, found: 310.20954.

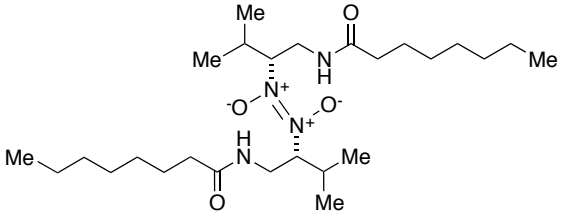
(*R*,*Z*)-2-methoxy-1-(3-methyl-1-octanamidobutan-2-yl)diazene 1-oxide (2.141):



(–)-Fragin (**2.80a**) (4.4 mg, 16.1 μmol, 1.0 eq) was dissolved in dry MeOH (0.20 mL) and Na_2CO_3 (2.05 mg, 19.3 μmol, 1.2 eq) was added and cooled to 0 °C. Dimethyl sulfate (1.7 μl, 17.7 μmol, 1.1 eq) was added and the mixture stirred at 0 °C for 15 minutes and then allowed to warm to r.t.

After 2.5 h, the mixture was diluted with water (0.2 mL) and then extracted with EtOAc (4 x 0.2 mL), the combined organic layers were dried over $MgSO_4$, filtered and evaporated. The residual was purified by flash column chromatography (SiO_2, pentane/EtOAc 2:1) to obtain methylated fragin **2.141** (3.15 mg, 11.4 µmol, 71%) as a colorless oil: $\mathbf{R_f}$ = 0.20 (SiO_2, pentane/EtOAc 2:1); **Optical rotation**: $[\alpha]_D^{25}$ = –8.7 (*c* 0.31, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3321, 2961, 2928, 2857, 1674, 1655, 1543, 1501, 1464, 1263, 1062, 1012, 801 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.90 (t, *J* = 5.7 Hz, 1H), 4.10 (td, *J* = 9.3, 3.2 Hz, 1H), 4.06 (s, 3H), 3.80 (ddd, *J* = 14.3, 6.0, 3.2 Hz, 1H), 3.56 (ddd, *J* = 14.3, 9.2, 6.1 Hz, 1H), 2.22 – 2.09 (m, 3H), 1.59 (quin., *J* = 7.1 Hz, 2H), 1.31 – 1.23 (m, 8H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.89 – 0.85 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 173.7, 78.7, 61.6, 39.4, 36.7, 31.8, 29.3, 29.2, 28.9, 25.9, 22.8, 19.3, 18.9, 14.2; **HRMS (ESI)** m/z calcd for $C_{14}H_{29}N_3O_3Na$ $[M+Na]^+$: 310.21011, found: 310.2999.

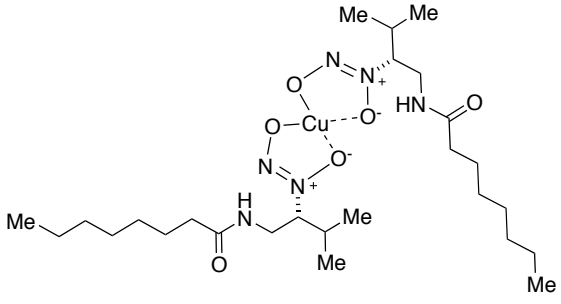
(*E*)-1,2-bis((*R*)-3-methyl-1-octanamidobutan-2-yl)diazene 1,2-dioxide (2.109):



Hydroxylamine **2.91a** (29.1 mg, 0.12 mmol, 1.0 eq) was dissolved in $CHCl_3$ (0.1 mL) and cooled to 0 °C. A solution of *m*-CPBA (32.3 mg, 0.13 mmol, 1.1 eq) in $CHCl_3$ (0.1 mL) was added and the mixture stirred at 0 °C for 2 h, and then 1 h at r.t. The mixture was diluted with $CHCl_3$ (0.2 mL) and washed with sat. aq. $NaHCO_3$ (3 x 0.1 mL) and brine (0.1 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to obtain the dimer **2.109** (103 mg, 61.0 µmol, quant.) as a white solid: **M**.**p**.: 90.8 – 91.5 °C; $\mathbf{R_f}$ = 0.37 (SiO_2, pentane/EtOAc 1:1); **Optical rotation**: $[\alpha]_D^{25}$ = +7.9 (*c* 0.47, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3377, 3259, 3072, 2953, 2923, 2870, 1636, 1546, 1465, 1377, 1266, 1203, 1039, 928, 802, 725, 679, 614 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.36 (bs, 2H), 5.21 (td, *J* = 7.9, 2.3 Hz, 2H), 3.85 – 3.79 (m, 2H), 3.64 – 3.57 (m, 2H), 2.30 – 2.22 (m, 2H), 2.17 (t, *J* = 7.8 Hz, 4H), 1.64 – 1.57 (m, 4H), 1.30 – 1.27 (m, 16H), 1.04 (d, *J* = 6.8 Hz, 6H), 0.95 (d, *J* = 6.6 Hz, 6H), 0.87 (t, *J* = 6.9 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ =

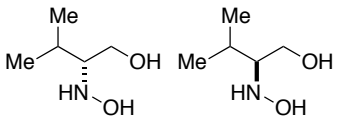
173.8, 72.5, 38.2, 36.6, 31.9, 29.4, 29.2, 28.3, 25.8, 22.8, 19.8, 18.5, 14.2; **HRMS (ESI)** m/z calcd for $C_{26}H_{53}N_4O_4$ $[M+H]^+$: 485.4061, found: 485.4063.

Cu-Fragin (2.144):



(–)-Fragin (**2.80a**) (2.24 mg, 8.2 μmol, 1.0 eq) was dissolved in dry MeOH (0.1 mL) and $Cu(OAc)_2$ (2.23 mg, 0.012 mmol, 1.5 eq) was added and the mixture stirred at r.t. for 18 h. Water (0.1 mL) was then added and the precipitate filtered over cotton and washed with water (3 x 0.1 mL). The filter was flushed with MeOH (1.0 mL) and the organic layer was dried over $NaSO_4$, filtered and evaporated to obtain Cu-fragin complex **2.144** (2.27 mg, 7.5 μmol, 91%) as a blue solid. **M.p.**: 154.2 – 154.9 °C; **FTIR (neat):** $\tilde{\nu}$ = 3270, 3074, 2959, 2926, 2858, 1638, 1552, 1408, 1465, 1408, 1348, 1277, 1248, 1179, 1124, 998, 934, 861, 796, 709 cm^{-1}; **HRMS (ESI)** m/z calcd for $C_{26}H_{53}Cu_1N_6O_6$ $[M+H]^+$: 608.3317, found: 608.3316; **UV-VIS:** λ_{max} = 238 nm; **X-ray crystal structure** is given in the appendices section.

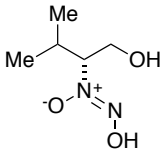
(*R*)-2-(hydroxyamino)-3-methylbutan-1-ol (2.107a) and
(*S*)-2-(hydroxyamino)-3-methylbutan-1-ol (2.107b):



2.107a **2.107b**

Was synthesized according to the literature of Breuning and co-workers and the data were in good agreement. [99]

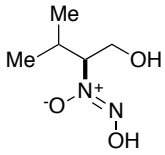
(*R*,*Z*)-2-hydroxy-1-(1-hydroxy-3-methylbutan-2-yl)diazene 1-oxide (valdiazen 2.105a):



Hydroxylamine **2.107a** (14.7 mg, 0.123 mmol, 1.0 eq) was dissolved in methanolic ammonia solution (7 N, 0.5 mL) and isopentyl nitrite (43.2 mg, 49.1 mL, 0.369 mmol, 3.0 eq) was added and the mixture stirred at r.t. The colorless solution immediately turned yellow. After 5 minutes a white solid precipitated. After 45 min, the mixture was evaporated and the residue dissolved in Et_2O (3.0 mL) and aq. NaOH (1

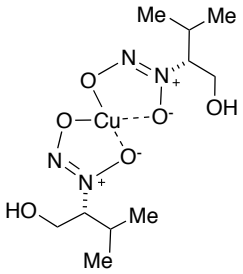
M, 0.7 mL) was added. The aq. layer was extracted with Et_2O (4 x 1.0 mL), acidified with aq. HCl (1 M) to pH = 1 and then extracted with Et_2O (4 x 1.0 mL). The combined organic layers were washed with brine (1.0 mL), dried over $MgSO_4$, filtered and evaporated to obtain valdiazen (**2.105a**) (8.44 mg, 0.057 mmol, 46%) as a white solid. **M.p.**: 51.4 – 51.9 °C; $\mathbf{R_f}$ = 0.07 (SiO_2, CH_2Cl_2/MeOH 20:1); **Optical rotation**: $[\alpha]_D^{25}$ = –1.5 (*c* 0.84, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3281, 3036, 2974, 2920, 2807, 1549, 1417, 1275, 1253, 1138, 1079, 1043, 1017, 927, 877, 859, 701, 643 cm^{-1}; **^{1}H NMR** (400 MHz, MeOD) δ = 4.04 – 3.96 (m, 2H), 3.87 – 3.80 (m, 1H), 2.18 – 2.06 (m, 1H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (101 MHz, MeOD) δ = 82.3, 61.2, 29.3, 19.4, 19.4; **HRMS (ESI)** m/z calcd for $C_5H_{12}N_2O_3Na$ $[M+Na]^+$: 171.07401, found: 171.07378; **X-ray crystal structure** is given in the appendices section.

(*S*,*Z*)-2-hydroxy-1-(1-hydroxy-3-methylbutan-2-yl)diazene 1-oxide (valdiazen 2.105b):



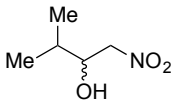
White solid (16.3 mg, 0.11 mmol, 41% from **2.107b**; **Optical rotation**: $[\alpha]_D^{25}$ = +1.0 (*c* 0.60, $CHCl_3$).

Cu-Valdiazen (2.145):



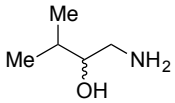
Fragin-NH_3 (**2.105c**) (5.81 mg, 35.0 μmol, 1.0 eq) was dissolved in dry MeOH (0.1 mL) and $Cu(OAc)_2$ (4.48 mg, 25.0 μmol, 0.7 eq) was added and the mixture stirred at r.t. for 15 h. The blue solution was diluted with H_2O (0.1 mL) and extracted with EtOAc (3 x 0.25 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to obtain the desired Cu-valdiazen complex (**2.145**) (6.14 mg, 34.0 μmol, 98%) as a blue solid. **M.p.**: 154.8 – 155.6 °C; **FTIR (neat):** $\tilde{\nu}$ = 3415, 2971, 2880, 1714, 1417, 1246, 1167, 1074, 1023, 935, 716, 692 cm^{-1}; **HRMS (ESI)** m/z calcd for $C_{10}H_{23}Cu_1N_4O_6$ $[M+H]^+$: 358.09081, found: 358.09049; **UV-VIS:** λ_{max} = 237 nm; **X-ray crystal structure** is given in the appendices section.

3-Methyl-1-nitrobutan-2-ol (2.87):



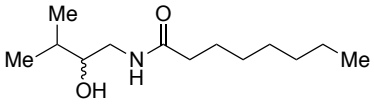
Isobutyraldehyde (**2.86**) (1.27 mL, 13.9 mmol, 1.0 eq) was dissolved in nitromethane (3.86 mL, 69.3 mmol, 5.0 eq) and freshly distilled NEt_3 (0.199 mL, 1.39 mmol, 0.1 eq) was added at r.t. over 10 min. The colorless solution turned slightly yellow. After 14 h, the mixture was evaporated and then purified by flash column chromatography (SiO_2, pentane/EtOAc 19:1) to yield the desired alcohol **2.87** as a colorless oil (1.74 g, 13.1 mmol, 94%). $\mathbf{R_f}$ = 0.16 (SiO_2, pentane/EtOAc 95:5); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.52 – 4.34 (m, 2H), 4.17 – 4.05 (m, 2H), 2.47 (s, 1H), 1.80 (m, 1H), 1.25 (td, J = 7.1, 0.7 Hz, 1H), 0.99 (dd, J = 6.8, 5.6 Hz, 6H); the data are in good agreement with the reported.[402]

1-amino-3-methylbutan-2-ol (2.88):



3-Methyl-1-nitrobutan-2-ol (**2.87**) (876 mg, 6.59 mmol, 1.0 eq) was dissolved in MeOH (70 mL). Pd/C (10% Pd, 701 mg, 0.658 mmol, 0.1 eq) was added and a H_2 ballon (1 bar) was placed. The reaction was allowed to stir at r.t. for 24. The mixture was filtered over Celite and the filter cake washed with MeOH. The solvent was evaporated to yield the desired amine **2.88** (550 mg, 3.36 mmol, 81%) as a colorless solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.26 (ddd, J = 9.3, 6.3, 3.1 Hz, 1H), 2.90 (dd, J = 12.6, 3.1 Hz, 1H), 2.57 (dd, J = 12.5, 9.1 Hz, 1H), 2.32 (s, 3H), 1.70 – 1.61 (m, 1H), 0.93 (dd, J = 22.6, 6.8 Hz, 6H); the data are in good agreement with the reported.[403]

***N*-(2-hydroxy-3-methylbutyl)octanamide (2.89):**



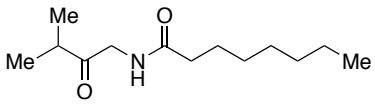
To a solution of 1-amino-3-methylbutan-2-ol (**2.88**) (550 mg, 5.33 mmol, 1.0 eq) in dry CH_2Cl_2 (27.5 mL) and DMF (2.75 mL), octanoic acid (0.844 mL, 5.33 mmol, 1.0 eq) and HATU (2.23 g, 5.86 mmol, 1.1 eq) were added. The solution was cooled to 0 °C and DIPEA (2.71 mL, 16.0 mmol, 3.0 eq) was added dropwise. The reaction was allowed to warm to r.t. and stirred

[402] J. A. Weeden, J. D. Chisholm, *Tetrahedron Lett*. **2006**, *47*, 9313.

[403] W. Jin, X. Li, Y. Huang, F. Wu, B. Wan, *Chem. Eur. J.* **2010**, *16*, 8259.

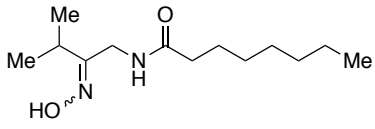
for 24 h. The reaction was quenched with aq. HCl (1 M, 5.0 mL) and extracted with EtOAc (3 x 5.0 mL). The combined organic layers were washed with aq. sat. $NaHCO_3$ (4.0 mL), water (3.0 mL) and brine (3.0 mL), dried over Na_2SO_4 and evaporated. The extract was purified by flash column chromatography (SiO_2, pentane/EtOAc 1:2) to yield the desired amide **2.89** as a colorless oil (964 mg, 4.21 mmol, 79%). $\mathbf{R_f}$ = 0.62 (SiO_2, pentane/EtOAc 1:2); **M.p.:** 47.8 – 48.5 °C; **FTIR (neat):** $\tilde{\nu}$ = 3308, 3212, 2957, 2926, 2858, 2326, 1634, 1555, 1465, 1354, 1258, 1143, 1070, 1013, 975, 845, 631 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.97 (s, 1H), 3.51 (ddd, *J* = 13.9, 6.6, 2.7 Hz, 1H), 3.42 (ddd, *J* = 8.7, 6.3, 2.7 Hz, 1H), 3.16 (ddd, *J* = 13.5, 8.4, 4.7 Hz, 1H), 2.36 (s, 1H), 2.22 – 2.19 (m, 2H), 1.75 – 1.59 (m, 3H), 1.33 – 1.25 (m, 8H), 0.95 (dd, *J* = 13.5, 6.8 Hz, 6H), 0.89 – 0.86 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 174.8, 43.8, 36.8, 32.3, 31.8, 29.4, 29.1, 25.9, 22.7, 18.7, 18.0, 14.2; **HRMS (ESI)** m/z calcd for $C_{13}H_{28}NO_2$ $[M+H]^+$: 230.2115, found 230.2118.

***N*-(3-methyl-2-oxobutyl)octanamide (2.85):**



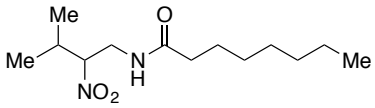
Alcohol **2.89** (964 mg, 4.21 mmol, 1.0 eq) and DMP (5.4 g, 12.6 mmol, 3.0 eq) were dissolved in CH_2Cl_2 (57 mL) and stirred at r.t. for 4 h. EtOAc (90 mL) was added and the organic layer was washed with aq. sat. $Na_2S_2O_3$ (15 mL), aq. sat. $NaHCO_3$ (2 x 10 mL) and brine (10 mL). The crude mixture was purified by flash column chromatography (SiO_2, pentane/EtOAc 1:3) to yield the desired ketone **2.85** (440 mg, 1.94 mmol, 46%) as a colorless solid. $\mathbf{R_f}$ = 0.16 (pentane/EtOAc 3:1); **FTIR (neat):** $\tilde{\nu}$ = 3318, 2954, 2855, 2336, 1716, 1637, 1532, 1468, 1385, 1236, 1102, 1022, 803, 645 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.21 (s, 1H), 4.21 (d, *J* = 4.3 Hz, 2H), 2.66 (hept, *J* = 7.0 Hz, 1H), 2.25 – 2.22 (m, 2H), 1.67 – 1.61 (m, 2H), 1.31 – 1.27 (m, 8H), 1.16 (d, *J* = 6.9 Hz, 6H), 0.89 – 0.86 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$,) δ = 209.5, 173.4, 47.4, 39.2, 36.7, 31.8, 29.4, 29.1, 25.8, 22.8, 18.3, 14.2; **HRMS (ESI)** m/z calcd for $C_{13}H_{26}NO_2$ $[M+H]^+$: 228.1958, found 228.1960.

***N*-(2-(hydroxyimino)-3-methylbutyl)octanamide (2.90):**



N-(3-Methyl-2-oxobutyl)octanamide (**2.85**) (793 mg, 3.49 mmol, 1.0 eq), NH_2OH x HCl (544 mg, 7.68 mmol, 2.2 eq) and NaOAc (555 mg, 6.63 mmol, 1.9 eq) were dissolved in MeOH (120 mL) and the mixture heated to 85 °C for 8 h. The solvent was removed under reduced pressure and water was added to the residue. The mixture was cooled to 0 °C and the resulting crystals were filtered off and dissolved in CH_2Cl_2. The solvent was evaporated and the residue was purified by flash column chromatography (SiO_2, pentane/EtOAc 3:1) to yield the desired product **2.90** (368 mg, 1.52 mmol, 44%) as a colorless solid. $\mathbf{R_f}$ = 0.33 (pentane/EtOAc 3:1); **FTIR (neat):** $\tilde{\nu}$ = 3302, 3092, 2959, 2925, 2850, 2459, 2361, 1636, 1555, 1460, 1413, 1327, 1261, 1224, 1096, 1031, 943, 798, 702, 616 cm^{-1}; **^{1}H NMR** (400 MHz, MeOD) δ = 4.09 (s, 2H), 2.54 (hept, *J* = 6.9 Hz, 1H), 2.20 (t, *J* = 7.5 Hz, 2H), 1.64 – 1.57 (m, 2H), 1.35 – 1.29 (m, 8H), 1.08 (d, *J* = 6.9 Hz, 6H), 0.90 (t, *J* = 6.7 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 176.1, 162.2, 36.9, 35.6, 32.9, 32.5, 30.2, 30.1, 27.0, 23.7, 20.4, 14.4; **HRMS (ESI)** m/z calcd for $C_{13}H_{27}N_2O_2$ $[M+H]^+$: 243.2067, found 243.2068.

***N*-(3-methyl-2-nitrobutyl)octanamide (2.108):**



Oxime (**2.90**) (8.0 mg, 33.0 μmol, 1.0 eq), Na_2HPO_4 (40.2 mg, 0.277 mmol, 8.4 eq) and powdered urea (11.1 mg, 0.182 mmol, 5.5 eq) were dissolved in dry ACN (0.45 mL) and heated to reflux for 30 minutes. The white mixture was allowed to cool to r.t. and *m*-CPBA (70%, 15.5 mg, 62.7 μmol, 1.9 eq) was added portionwise over 2 minutes. The white mixture was heated to reflux for 2 h. The mixture was allowed to cool to r.t., filtered over cotton and rinsed with ACN. The colorless solution was evaporated, the residue suspended in CH_2Cl_2 and washed with sat. aq. $NaHCO_3$ (0.3 mL), sat. aq. $Na_2S_2O_3$ (0.3 mL) and water (0.3 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash column chromatography (SiO_2, pentane/EtOAc 6:1 to 4:1) to yield the desired nitro compound **2.108** as a colorless oil (4.63 mg, 18.0 μmol, 54%). $\mathbf{R_f}$ = 0.17

(pentane/EtOAc 4:1); **FTIR (neat):** $\tilde{\nu}$ = 3281, 2957, 2927, 2857, 1650, 1549, 1465, 1363, 1269, 792, 670, 628 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.74 (s, 1H), 4.50 (ddd, *J* = 10.2, 7.5, 2.8 Hz, 1H), 3.93 (ddd, *J* = 14.6, 6.7, 2.8 Hz, 1H), 3.49 (ddd, *J* = 14.4, 10.0, 5.5 Hz, 1H), 2.28 – 2.20 (m, 2H), 2.17 – 2.14 (m, 2H), 1.63 – 1.56 (m, 2H), 1.31 – 1.23 (m, 8H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 173.8, 93.4, 39.8, 36.6, 31.8, 30.8, 29.3, 29.1, 25.7, 22.7, 19.0, 18.7, 14.2; **HRMS (ESI)** m/z calcd for $C_{13}H_{27}N_2O_3$ $[M+H]^+$: 259.2016, found: 259.2015.

Isolation of valdiazen (2.105):

The yellow supernatant (500 mL, hamF mutant) was set to pH 11 with aq. NaOH (1.0 M, 150 mL) and the aq. layer was extracted with CH_2Cl_2 (3 x 150 mL). The organic layer was discarded. The basic aq. layer was set to pH 4.0 with aq. HCl (1.0 M) and then extracted with CH_2Cl_2 (3 x 200 mL) and the combined organic layers were dried over Na_2SO_4, filtered and evaporated to obtain a yellow oil. Further purifications were performed by HPLC.

Column:	Synergi 4u Hydro-RP 80Å, 250 x 4.6 mm, 4 micron (Phenomenex)
Mobile Phase A:	20 mM aq. NH_4OAc (pH = 4.0)
Mobile Phase B:	acetonitrile
Flow rate:	1.0 mL/min
Column temperature:	40 °C
Decection (DAD):	220 nm
Retention time valdiazen:	9.5 – 10 min (broad peak)
Eluent program:	0 min 2% B; 15 min 50% B; 22.1 min 100% B

The isolated fractions were evaporated to dryness and the isolate was dissolved in CH_2Cl_2, filtered over wool and evaporated to dryness to yield 0.5 mg of pure valdiazen (**2.105**).

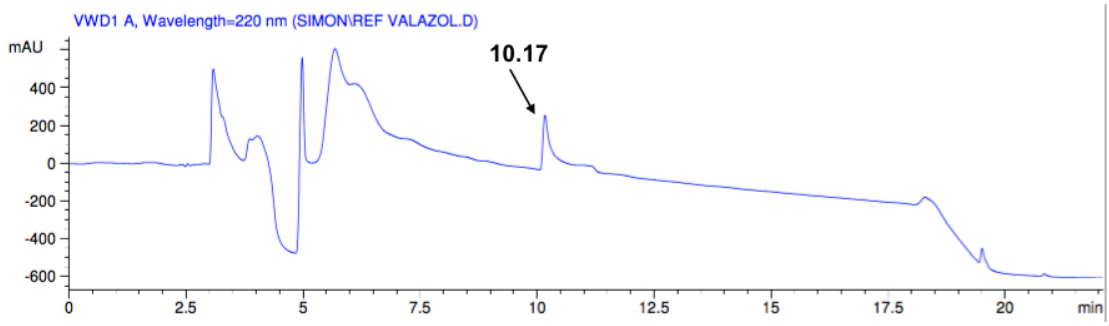


Figure 7.1: HPLC-trace of synthetic valdiazen (**2.105**).

Chiral HPLC measurement conditions for valdiazen (2.105):

Column:	Chiralpak OD-H, 250 x 4.6 mm, 10 μm (Daicel, cat. No. DAIC14325)
Mobile Phase:	hexane/EtOH (8:2)
Isocratic Eluent:	hexane/EtOH (8:2)
Flow rate:	0.8 mL/min
Column temperature:	38 °C
Decection (DAD):	228 nm (BW 6 nm)
Injection volume:	5 μL
Sample conc.:	2.0 mg/mL MeOH

pKa-measurement of valdiazen (2.105):

Endpunkte

DET pH **DET pH 6.1**

EP1	8.713	pH	6.7098	mL
EP2	3.940	pH	10.1048	mL
HP1	11.707	pH	3.3549	mL
HP2	5.516	pH	8.4073	mL

Resultate

Gehalt	**192.80**	**%**
Titer 0,1 N HCl	**1.0023**	
Anzahl Bestimmungen (n)	**1**	
Mittelwert	**192.80**	**%**
Rel Standardabweichung	**ungültig**	**%**

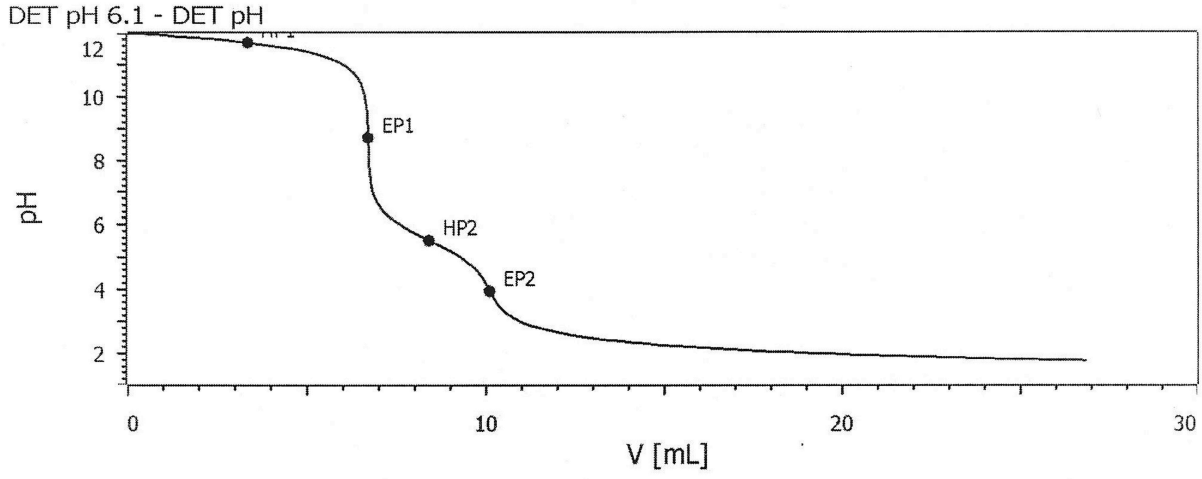


Figure 7.2: pka-mesruements of valdiazen (**2.105**).

NO-release measurements of (–)-fragin (2.80a):

A stock solution of 5 mg DAN in $CHCl_3$:AcOH (50 mL; 45:5) was prepared. To the DAN-stock solution (4.0 mL) (–)-fragin (**2.80a**) (0.8 mg) was added and the mixture sonicated for 10 minutes. Three separate samples (each 1.0 mL) were quenched with NaOH (1 M, 3.0 mL) after 1 h, 5 h and 24 h and the fluorescence was measured; (excitation = 365 nm, emission = 405 nm; DAN = 2,3-diaminonaphthalene; WAA = water acetic acid mixture).
$NaNO_2$ was used as a positive control.

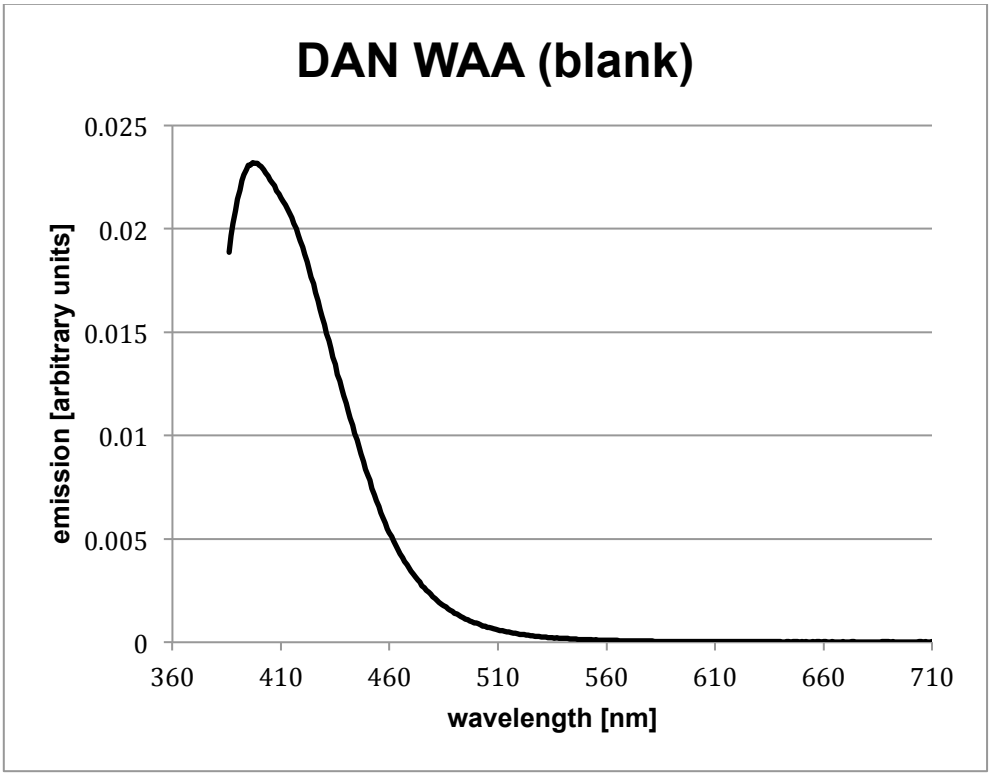


Figure 7.3: DAN-stock solution.

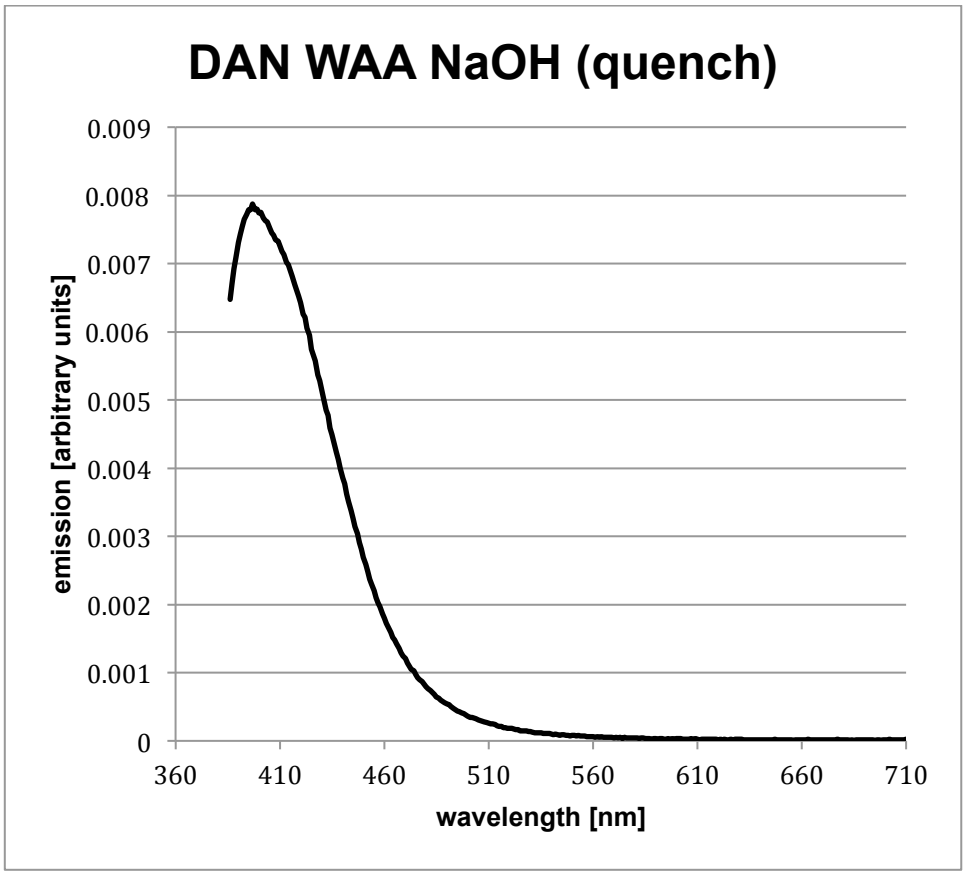


Figure 7.4: Quenched DAN-solution (negative control).

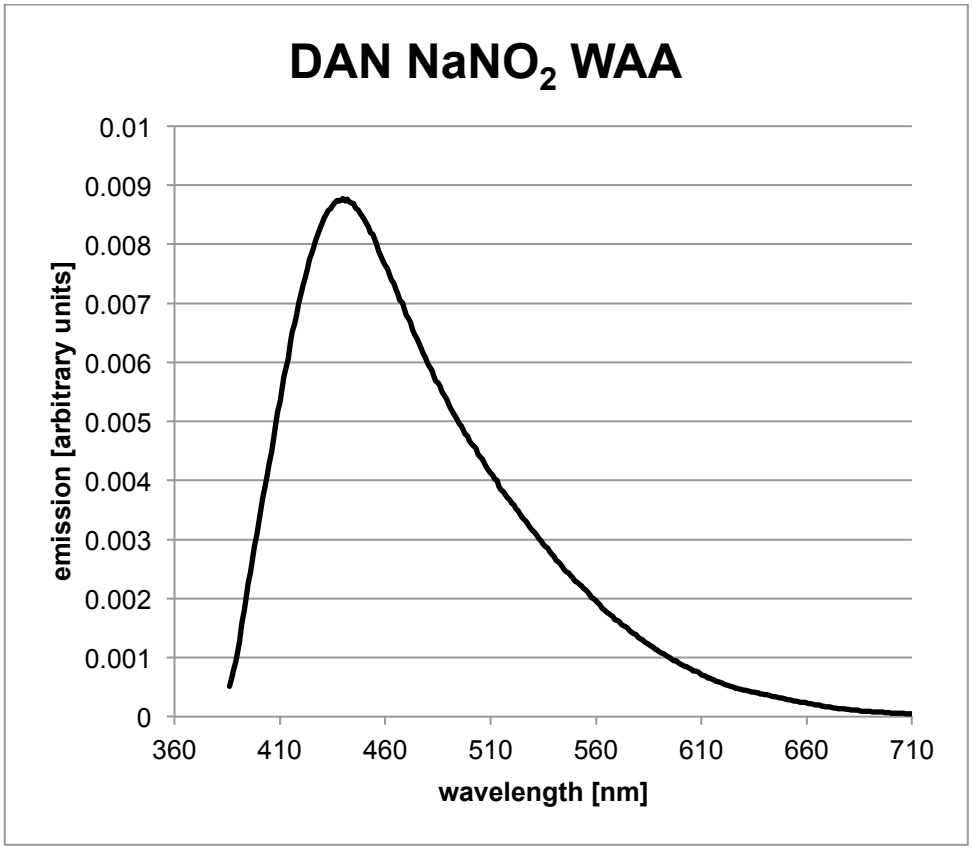


Figure 7.5: $NaNO_2$-DAN-solution.

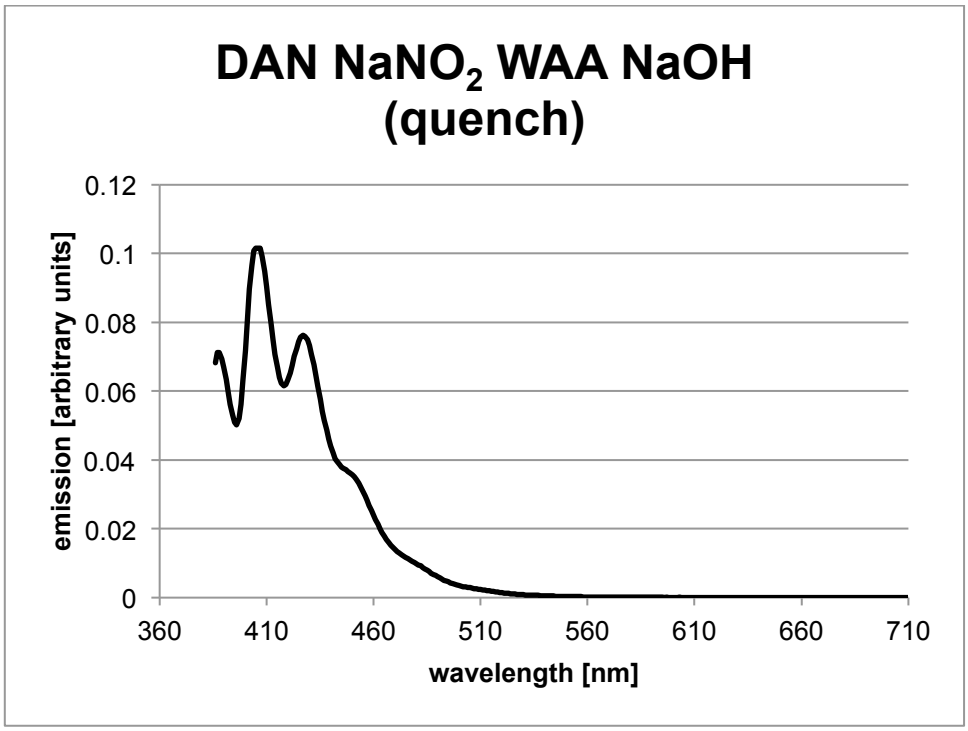


Figure 7.6: Quenched $NaNO_2$-DAN-solution (positive control).

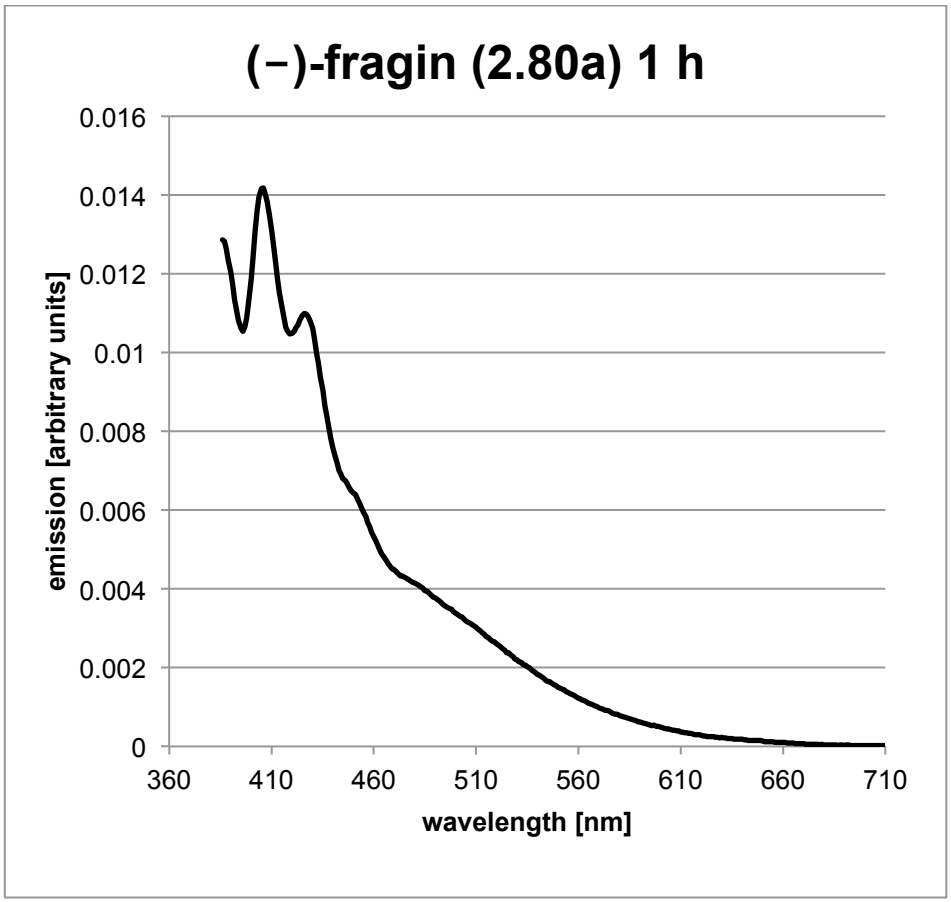


Figure 7.8: Quenched Fragin-DAN-solution after 1 h.

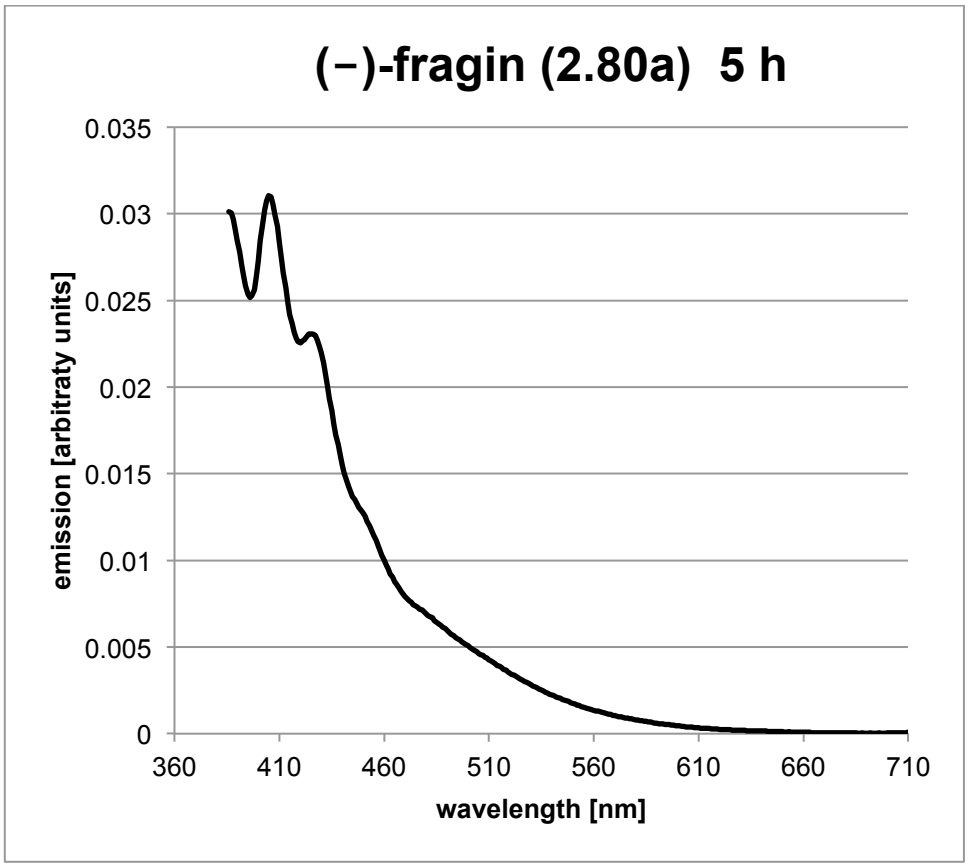


Figure 7.9: Quenched Fragin-DAN-solution after 5 h.

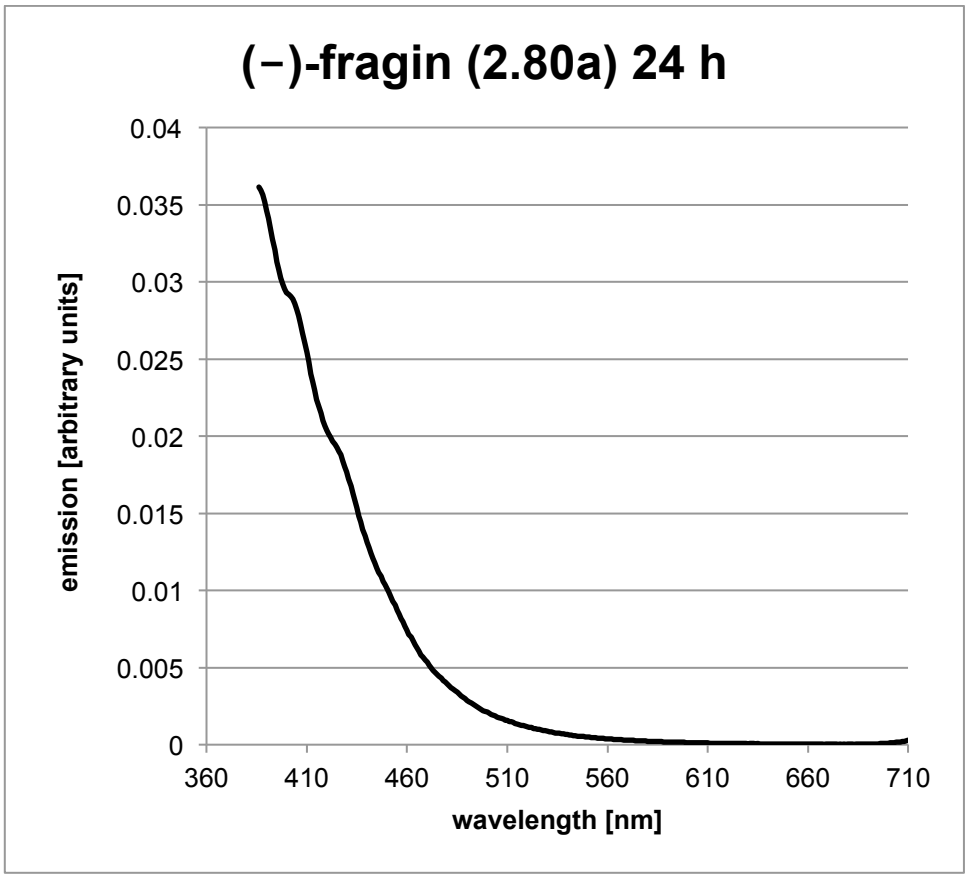


Figure 7.10: Quenched Fragin-DAN-solution after 24 h.

UV-VIS measurements of Cu-fragin (2.144) and Cu-valdiazen (2.145).

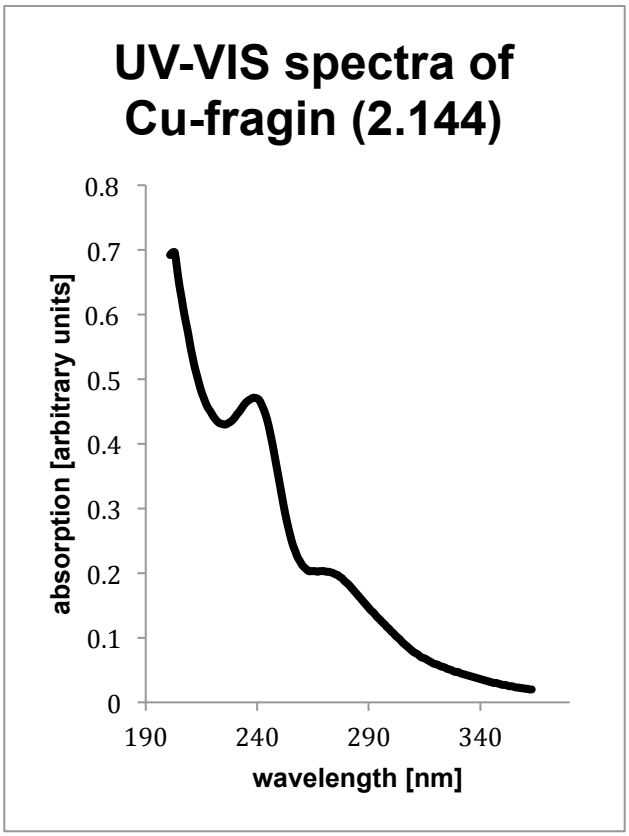


Figure 7.11: UV-VIS spectra of Cu-fragin complex (**2.144**) (λ_{max} = 238 nm)

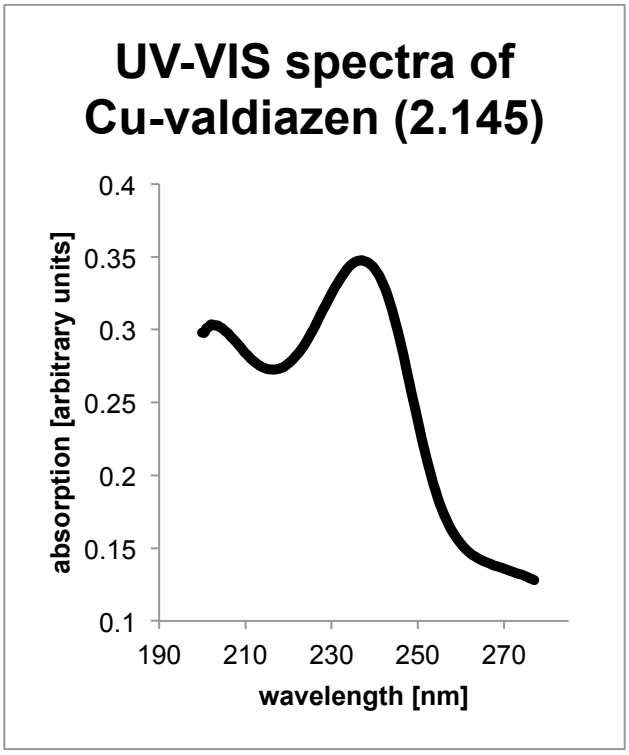
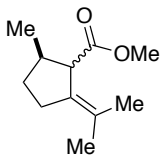


Figure 7.12: UV-VIS spectra of Cu-valdiazen complex (**2.145**) (λ_{max} = 237 nm)

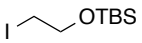
7.3 Synthetic Studies Towards (2*R*)-Hydroxynorneomajucin

Methyl (2*R*)-2-methyl-5-(propan-2-ylidene)cyclopentane-1-carboxylate (3.118):



(*R*)-(+)-Pulegone (**3.83**) (20.0 g, 121 mmol, 1.0 eq) and $NaHCO_3$ (3.05 g, 36.3 mmol, 0.3 eq) were dissolved in Et_2O (150 ml). The reaction mixture was stirred at 0 °C and Br_2 (19.4 g, 6.2 ml, 121 mmol, 1.0 eq) was added dropwise over a period of 30 min. The mixture was stirred for another 30 min at this temperature, filtered and transferred into a cold solution of NaOMe (25% in MeOH, 64 ml, 280 mmol, 2.3 eq). The mixture was stirred at reflux for 3 h and then cooled to r.t. The reaction was quenched with aq. HCl (1 M, 80 ml) and the aqueous layer was extracted with Et_2O (3 x 100 ml). The combined organic layers were washed wih brine (60 ml), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The extract was purified by flash column chromatography (SiO_2, pentane/Et_2O 50:1) to afford a diastereomeric mixture of alkene **3.118** (17.6 g, 96.6 mmol, 80%, d.r. = 1:1) as a slightly yellow oil. The analytic data is in good agreement with the literature.[404]

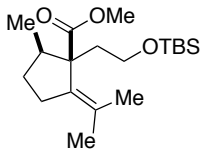
***tert*-Butyl(2-iodoethoxy)dimethylsilane (3.138):**



Iodoethanol (15.5 g, 90.0 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (250 ml). Imidazole (9.38 g, 135 mmol, 1.5 eq) and TBSCl (15.2 g, 99.0 mmol, 1.1 eq) were added and the mixture was stirred at r.t. for 16 h. The reaction mixture was washed with water (2 x 50 ml) and brine (2 x 50 ml), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to afford silyl ether **3.138** (25.3 g, 88.0 mmol, 98%) as a colorless liquid. The analytic data is in good agreement with the literature.[205]

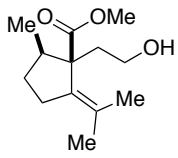
[404] T. Hudlicky, R. P. Short, *J. Org. Chem.* **1982**, *47*, 1522.

Methyl (1*R*,2*R*)-1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-methyl-5-(propan-2-ylidene)-cyclopentane-1-carboxylate (3.139):



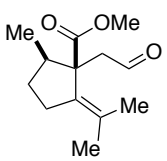
Freshly distilled diisopropylamine (20.0 ml, 135 mmol, 1.4 eq) was added to THF (50 ml) and cooled to –78 °C. *n*-BuLi (1.6 M in hexane, 79.0 ml, 126 mmol, 1.3 eq) was slowly added and the solution stirred for 15 min at this temperature. The reaction mixture was allowed to warm to 0 °C and was stirred for 1 h at this temperature. The solution was cooled to –78 °C and ester **8** (17.6 g, 97.0 mmol, 1.0 eq) and DMPU (62.0 g, 59.0 ml, 483 mmol, 5.0 eq) was added slowly and the solution stirred for 15 min at this temperature and then stirred for 1 h at 0 °C. The yellow mixture was cooled to –78 °C and a solution of **3.118** (33.2 g, 116 mmol, 1.2 eq) in THF (50 ml) was added. The mixture was stirred for 1 h at this temperature and then allowed to warm to r.t. over 1 h. The reaction was quenched with aq. HCl (1 M, 200 ml). The aqueous layer was extracted with Et_2O (4 x 150 ml). The combined organic layers were washed with brine (100 ml), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The extract was purified by flash column chromatography (SiO_2, pentane/Et_2O 40:1, then 20:1 and 8:1) to afford alkylated ester **3.139** (25.3 g, 74.4 mmol, 77%) as a yellow oil. $\mathbf{R_f}$ = 0.24 (SiO_2, pentane/Et_2O 40:1); **Optical rotation**: $[\alpha]_D^{25}$ = +37.8 (*c* 0.790, $CHCl_3$); **FTIR (neat)**: $\tilde{\nu}$ = 2953, 2933, 2858, 1727, 1462, 1434, 1253, 1218, 1186, 1155, 1095, 1004, 837, 775, 631 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.63 (s, 3H), 3.62 – 3.53 (m, 2H), 2.49 (dd, *J* = 15.4, 7.3 Hz, 1H), 2.29 – 2.17 (m, 2H), 2.17 – 2.04 (m, 1H), 1.96 (ddd, *J* = 14.2, 9.0, 6.4 Hz, 1H), 1.77 – 1.69 (m, 1H), 1.64 (d, *J* = 1.7 Hz, 3H), 1.62 – 1.53 (m, 1H), 1.50 (d, *J* = 1.7 Hz, 3H), 0.90 – 0.89 (m, 3H), 0.88 (s, 9H), 0.03 (d, *J* = 1.7 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 176.6, 137.7, 125.0, 60.4, 57.2, 51.4, 44.6, 36.9, 32.6, 32.2, 26.1, 22.4, 20.6, 18.4, 14.9, –5.1, –5.1; **HRMS (ESI)** m/z calcd. for $C_{19}H_{37}O_3Si$ $[M+H]^+$ 341.2506, found: 341.2507.

Methyl (1*R*,2*R*)-1-(2-hydroxyethyl)-2-methyl-5-(propan-2-ylidene)-cyclopentane-1-carboxylate (3.140):



TBS-protected alcohol **3.139** (2.32 g, 6.81 mmol, 1.0 eq) was dissolved in THF (50 ml) and cooled to 0 °C. Acetic acid (1.0 ml) and TBAF (5.99 g, 6.81 mmol, 1.0 eq) were added slowly. The solution was allowed to warm to r.t. and stirred for 18 h. The solution was cooled to 0 °C and quenched with aq. sat. $NaHCO_3$ (80 ml). The aqueous layer was extracted with Et_2O (3 x 100 ml) and the combined organic layers were washed with brine (50 ml). The organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, pentane/Et_2O 1:1) to obtain alcohol **3.139** (1.22 g, 5.39 mmol, 79%) as slightly yellow oil. $\mathbf{R_f}$ = 0.27 (SiO_2, pentane/Et_2O 1:1); **Optical rotation**: $[\alpha]_D^{26}$ = +35.4 (*c* 0.432, $CHCl_3$); **FTIR (neat)**: $\tilde{\nu}$ = 3428, 2952, 2334, 1725, 1457, 1226, 1032, 891, 768 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.75 – 3.62 (m, 2H), 3.66 (s, 3H), 2.52 (dd, *J* = 15.6, 7.1 Hz, 1H), 2.29 – 1.99 (m, 5H), 1.83 – 1.74 (m, 1H), 1.65 (d, *J* = 1.9 Hz, 3H), 1.54 (dd, *J* = 2.8, 1.0 Hz, 3H), 1.53 – 1.46 (m, 1H), 0.92 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 177.3, 138.7, 125.5, 59.9, 57.4, 51.7, 44.6, 37.8, 32.8, 32.0, 22.5, 20.7, 15.3; **HRMS (ESI)** m/z calcd. for $C_{13}H_{23}O_3$ $[M+H]^+$: 227.1642, found: 227.1642.

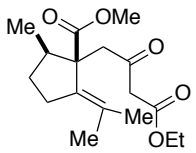
Methyl (1*R*,2*R*)-2-methyl-1-(2-oxoethyl)-5-(propan-2-ylidene)-cyclopentane-1-carboxylate (3.141):



Alcohol **3.140** (3.35 g, 14.8 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (150 ml). DMP (7.05 g, 16.3 mmol, 1.1 eq) was added and the reaction mixture was stirred for 2 h at r.t. Sat. aq. $NaHCO_3$ (50 ml) was added and the aqueous layer was extracted with CH_2Cl_2 (5 x 50 ml). The combined organic layers were washed with brine (25 ml), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography (SiO_2, pentane/Et_2O 4:1) to obtain aldehyde **3.141** (2.95 g, 13.2 mmol, 89%) as a colorless oil. $\mathbf{R_f}$ = 0.38 (SiO_2, pentane/Et_2O 5:1); **Optical rotation**: $[\alpha]_D^{25}$ = +23.6 (*c* 0.591, $CHCl_3$); **FTIR (neat)**: $\tilde{\nu}$ = 2952, 2735, 2361, 1722, 1457, 1222,

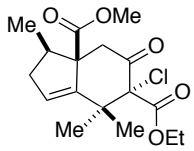
1058, 892, 767 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.66 (t, *J* = 2.9 Hz, 1H), 3.68 (s, 3H), 2.93 (dd, *J* = 16.1, 2.8 Hz, 1H), 2.74 (dd, *J* = 16.1, 3.1 Hz, 1H), 2.56 (dd, *J* = 15.8, 7.5 Hz, 1H), 2.31 – 2.13 (m, 2H), 1.89 – 1.79 (m, 1H), 1.66 (d, *J* = 1.7 Hz, 3H), 1.61 (m, 1H), 1.56 (dd, *J* = 2.6, 1.1 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 202.5, 175.3, 137.4, 126.6, 56.2, 51.9, 48.3, 45.9, 32.6, 32.0, 22.6, 20.7, 14.6; **HRMS (ESI)** m/z calcd. for $C_{13}H_{21}O_3$ $[M+H]^+$: 225.1485, found: 225.1485.

Methyl (1*R*,2*R*)-1-(4-ethoxy-2,4-dioxobutyl)-2-methyl-5-(propan-2-ylidene)cyclopentane-1-carboxylate (3.134):



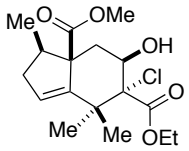
Ethyl diazoacetate (3.07 g, 26.4 mmol, 2.0 eq) was dissolved in CH_2Cl_2 (25 ml), $SnCl_2$ (255 mg, 1.32 mmol, 0.1 eq) was added and the reaction mixture was stirred at r.t. A solution of aldehyde **3.141** (2.95 g, 13.2 mmol, 1.0 eq) in CH_2Cl_2 (30 ml) was added dropwise. The mixture turned yellow and formation of N_2 was observed. The reaction mixture was stirred for 12 h at r.t., then it was diluted with CH_2Cl_2 (50 ml), filtrered over Celite and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography (SiO_2, pentane/Et_2O 7:1 to 2:1) to obtain the β-ketoester **3.134** (3.82 g, 12 mmol, 24.6 mmol, 93%, keto/enol form 10:1) as a slightly orange oil. **R_f** = 0.24 (SiO_2, pentane/Et_2O 5:1); **Optical rotation**: $[\alpha]_D^{25}$ = +49.6 (*c* 0.748, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 2950, 1717, 1644, 1454, 1306, 1224, 1183, 1155, 1033 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.17 (q, *J* = 7.1 Hz, 2H), 3.65 (d, *J* = 1.8 Hz, 3H), 3.41 (d, *J* = 5.5 Hz, 2H), 3.23 (d, *J* = 16.7 Hz, 1H), 2.95 (d, *J* = 16.7 Hz, 1H), 2.57 – 2.41 (m, 2H), 2.41 – 2.25 (m, 1H), 1.85 – 1.73 (m, 1H), 1.66 – 1.61 (m, 3H), 1.55 – 1.46 (m, 1H), 1.52 (d, *J* = 1.5 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.85 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 201.2, 175.8, 167.3, 138.5, 124.6, 61.4, 56.9, 51.7, 50.8, 46.6, 43.6, 32.8, 31.9, 22.5, 20.5, 14.7, 14.2; **HRMS (ESI)** m/z calcd. for $C_{17}H_{27}O_5$ $[M+H]^+$: 311.1853, found: 311.1855.

6-Ethyl 3a-methyl (3*R*,3a*R*,6*R*)-6-chloro-3,7,7-trimethyl-5-oxo-2,3,4,5,6,7-hexahydro-3a*H*-indene-3a,6-dicarboxylate (3.142):



β-Ketoester **3.134** (40.0 mg, 129 µmol, 1.0 eq) was dissolved in degassed Ac_2O (3.0 ml, thaw freeze method, 3 cycles). Flame-dried LiCl (54.7 mg, 1.29 mmol, 10 eq) was added and the reaction mixture was heated to 50 °C. $Mn(OAc)_3 \cdot 2\ H_2O$ (141 mg, 516 µmol, 4.0 eq) was added and the reaction mixture was stirred for 5 h at this temperature. Water (5 ml) was added and the mixture was extracted with EtOAc (5 x 5 ml). The combined organic layers were washed with brine (5 ml), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, pentane/Et_2O 6:1 to 3:1) to obtain oxo-dicarboxylate **3.142** (17.1 mg, 50.3 µmol, 39%) as a white solid. **M.p.**: 66.7 – 67.4 °C; $\mathbf{R_f}$ = 0.26 (SiO_2, pentane/Et_2O 6:1); **Optical rotation**: $[\alpha]_D^{26}$ = –53.2 (*c* 0.730, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 2982, 2931, 1728, 1459, 1408, 1385, 1366, 1346, 1246, 1225, 1105, 1034, 979, 894, 833, 757, 708, 606 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.91 – 5.90 (m, 1H), 4.36 – 4.21 (m, 2H), 3.68 (s, 3H), 3.49 (d, *J* = 15.3 Hz, 1H), 2.99 (d, *J* = 15.5 Hz, 1H), 2.55 – 2.42 (m, 2H), 2.35 – 2.23 (m, 1H), 1.38 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.21 (s, 3H), 0.97 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 199.7, 173.9, 165.8, 146.1, 129.9, 79.0, 62.7, 60.2, 52.1, 50.8, 45.2, 43.6, 39.2, 24.1, 22.1, 14.2, 14.1; **HRMS (ESI)** m/z calcd. for $C_{17}H_{24}O_5Cl$ $[M+H]^+$: 343.1307, found: 343.1308.

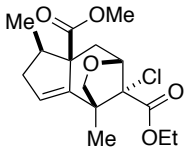
6-Ethyl 3a-methyl (3*R*,3a*R*,5*R*,6*R*)-6-chloro-5-hydroxy-3,7,7-trimethyl-2,3,4,5,6,7-hexahydro-3a*H*-indene-3a,6-dicarboxylate (3.143):



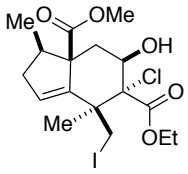
A solution of oxo-dicarboxylate **3.142** (1.05 g, 3.05 mmol, 1.0 eq) was dissolved in MeOH (50 ml) and cooled to 0 °C and $NaBH_4$ (294 mg, 7.63 mmol, 2.5 eq) was added in small portions. The reaction mixture was stirred at 0 °C for 1 h, then the cooling bath was removed and the reaction mixture was stirred at r.t. for 3 h. The reaction mixture was cooled to 0 °C and quenched with brine (50 ml). The aqueous layer was extracted with EtOAc (5 x 50 ml) and the combined organic layers were washed with brine (30 ml), dried over Na_2SO_4, filtered

and evaporated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, pentane/Et_2O 6:1 to 3:1) to afford hydroxy-dicarboxylate **3.143** (904 mg, 2.62 mmol, 86%) as a white solid. **M.p.**: 82.1 – 83.0 °C; **R_f** = 0.14 (SiO_2, pentane/Et_2O 6:1); **Optical rotation**: $[\alpha]_D^{25}$ = +42.4 (*c* 0.282, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3457, 2967, 2929, 2338, 1734, 1692, 1450, 1409, 1384, 1363, 1284, 1239, 1193, 1105, 1088, 1032, 995, 912, 887, 853, 819, 757, 702, 627 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.87 (dd, *J* = 3.2, 1.7 Hz, 1H), 4.50 (s, 1H), 4.36 – 4.21 (m, 3H), 3.69 (s, 3H), 2.88 (dd, *J* = 14.7, 2.8 Hz, 1H), 2.42 (ddd, *J* = 14.9, 7.4, 3.1 Hz, 1H), 2.32 – 2.20 (m, 1H), 2.17 (ddd, *J* = 14.9, 10.3, 1.7 Hz, 1H), 2.03 (dd, *J* = 14.8, 3.7 Hz, 1H), 1.53 (s, 3H), 1.38 – 1.31 (m, 6H), 0.97 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 176.6, 170.7, 147.6, 129.6, 75.0, 74.2, 62.2, 56.4, 51.7, 49.9, 42.3, 38.9, 35.8, 26.5, 26.1, 14.7, 14.1; **HRMS (ESI)** m/z calcd. for $C_{17}H_{26}O_5Cl$ $[M+H]^+$: 345.1463, found: 345.1462; **X-ray crystal structure** is given in the appendices section.

9-Ethyl 5a-methyl (1*R*,4*R*,5a*R*,6*R*,9*R*)-9-chloro-1,6-dimethyl-1,2,4,5,6,7-hexahydro-5a*H*-1,E-methanocyclopenta[*d*]oxepine-5a,9-dicarboxylate (3.144) and 6-ethyl 3a-methyl (3*R*,3a*R*,5*R*,6*R*,7*S*)-6-chloro-5-hydroxy-7-(iodomethyl)-3,7-dimethyl-2,3,4,5,6,7-hexahydro-3a*H*-indene-3a,6-dicarboxylate (3.146):



3.144

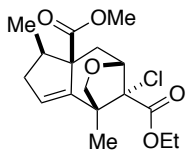


3.146

Hydroxy-dicarboxylate **3.143** (872 mg, 2.53 mmol, 1.0 eq) was dissolved in degassed cyclohexane (48 ml, thaw freeze method, 3 cycles) and $Pb(OAc)_4$ (872 mg, 10.1 mmol, 4.0 eq), iodine (1.97 g, 7.59 mmol, 3.0 eq) and $CaCO_3$ (1.03 g, 10.1 mmol, 4.0 eq) were added. The reaction mixture was stirred at r.t. and irradiated using a low pressure Hg-lamp for 8 h. The violet reaction mixture was cooled to 0 °C and sat. aq. $Na_2S_2O_3$ (50 ml) was added until the mixture turned colorless. The mixture was extracted with EtOAc (4 x 25 ml), washed with brine (25 ml), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The extract was purified by flash column chromatography SiO_2, (pentane/Et_2O 5:1 to 3:1) to afford chloro-furan **3.144** (507 mg, 1.48 mmol, 58%) as colorless

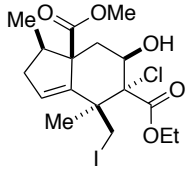
solid and the iodo compound **3.146** (87 mg, 17.7 µmol, 7%) as a colorless light sensitive oil.

Chloro-furan 3.144: **M.p.**: 96.5 - 97.1 °C; **R_f** = 0.16 (SiO_2, pentane/Et_2O 4:1);



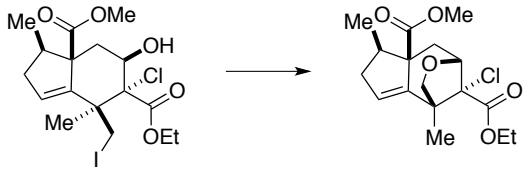
Optical rotation: $[\alpha]_D^{25}$ = –50.5 (*c* 0.372, $CHCl_3$); **FTIR (neat)**: $\tilde{\nu}$ = 2961, 2945, 2906, 2360, 1736, 1721, 1453, 1383, 1228, 1081, 1031, 981, 936, 876, 772, 726 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.83 (s, 1H), 4.71 (d, *J* = 4.8 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 1H), 3.85 (dd, *J* = 8.1, 0.8 Hz, 1H), 3.72 – 3.66 (m, 3H), 3.59 (d, *J* = 8.2 Hz, 1H), 3.07 (dd, *J* = 14.4, 4.9 Hz, 1H), 2.46 – 2.32 (m, 2H), 2.21 – 2.02 (m, 1H), 1.90 (d, *J* = 14.2 Hz, 1H), 1.35 (s, 3H), 1.29 (td, *J* = 7.1, 0.8 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 173.8, 168.5, 145.6, 129.8, 79.6, 73.7, 73.6, 62.4, 57.5, 51.8, 49.5, 48.7, 39.4, 37.0, 15.1, 14.1, 13.4; **HRMS (ESI)** m/z calcd. for $C_{17}H_{23}O_5ClNa$ $[M+Na]^+$: 365.1126, found: 365.1125; **X-ray crystal structure** is given in the appendices section.

Iodo compound 3.146: **R_f** = 0.31 (SiO_2, pentane/Et_2O 4:1); **Optical rotation**:



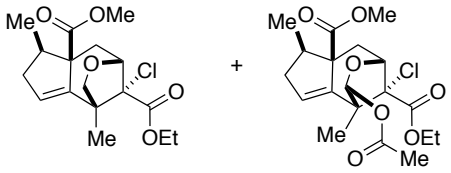
$[\alpha]_D^{25}$ = +39.2 (*c* 0.607, $CHCl_3$); **FTIR (neat)**: $\tilde{\nu}$ = 3481, 2955, 2360, 1735, 1435, 1378, 1228, 1092, 1033, 888, 796, 734 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.98 (d, *J* = 2.5 Hz, 1H), 4.54 (q, *J* = 2.9 Hz, 1H), 4.45 (d, *J* = 3.3 Hz, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 3.91 (d, *J* = 10.5 Hz, 1H), 3.74 (d, *J* = 0.7 Hz, 3H), 3.67 (d, *J* = 10.5 Hz, 1H), 2.85 (dd, *J* = 14.8, 2.7 Hz, 1H), 2.46 – 2.38 (m, 1H), 2.34 – 2.23 (m, 2H), 2.10 (dd, *J* = 14.9, 3.7 Hz, 1H), 1.69 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 0.98 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 176.9, 170.0, 142.1, 134.9, 73.8, 71.1, 62.7, 56.1, 52.1, 50.6, 46.0, 38.8, 35.5, 26.5, 16.5, 14.4, 14.0; **HRMS (ESI)** m/z calcd. for $C_{17}H_{24}O_5IClNa$ $[M+Na]^+$: 493.0249, found: 493.0254.

Cyclization of iodo compound 3.146 to chloro-furan 3.144:



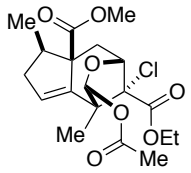
Iodo compound **3.146** (6.83 mg, 14.5 µmol, 1.0 eq) was dissolved in acetone (0.5 ml) and covered with aluminum foil. AgOAc (4.7 mg, 43.5 µmol, 3.0 eq) was added and the reaction mixture was heated to 65 °C for 12 h. After cooling to r.t., the reaction mixture was filtered over Celite and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, pentane/Et_2O 4:1) to afford chloro-furan **3.144** (4.3 mg, 0.11 mmol, 88%) as a colorless solid.

9-Ethyl 5a-methyl (1*R*,4*R*,5a*R*,6*R*,9*R*)-9-chloro-1,6-dimethyl-1,2,4,5,6,7-hexahydro-5a*H*-1,4-methanocyclopenta[*d*]oxepine-5a,9-dicarboxylate (3.144) and 9-Ethyl 5a-methyl (1*R*,2*R*,4*R*,5a*R*,6*R*,9*R*)-2-acetoxy-9-chloro-1,6-dimethyl-1,2,4,5,6,7-hexahydro-5a*H*-1,4-methanocyclopenta[*d*]-oxepine-5a,9-dicarboxylate (3.145)



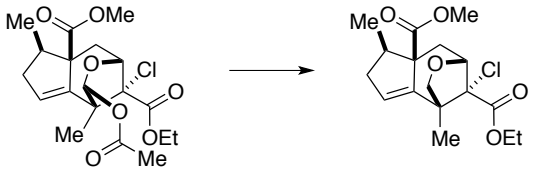
3.144 **3.145**

Hydroxy-dicarboxylate **3.143** (3.48 g, 10.1 mmol, 1.0 eq) was dissolved in degassed cyclohexane (200 ml, thaw freeze method, 3 cycles). $Pb(OAc)_4$ (11.5 g, 25.2 mmol, 2.5 eq), iodine (6.54 g, 25.2 mmol, 2.5 eq) and $CaCO_3$ (4.04 g, 40.4 mmol, 4.0 eq) were added. The reaction mixture was stirred at r.t. and irradiated using a low pressure Hg-lamp for three days and $Pb(OAc)_4$ (45.7 g, 101 mmol, 10 eq), iodine (26.2 g, 101 mmol, 10 eq) and $CaCO_3$ (10.3 g, 101 mmol, 10 eq) were added in four equal portions (each 2.5 eq) during this time. The violet reaction mixture was cooled to 0 °C and sat. aq. $Na_2S_2O_3$ (400 ml) was added until the mixture turned colorless. The mixture was extracted with EtOAc (4 x 200 ml), washed with brine (100 ml), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, pentane/Et_2O 5:1 to 3:1) to afford chloro-furan **3.144** (2.82 g, 8.2 mmol, 81%) as a colorless solid and furan-acetate **3.145** (600 mg, 1.5 mmol, 15%) as a colorless solid.



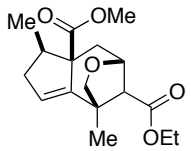
Acetyl-furan 3.145: M.p.: 130.5 – 131.5 °C; $\mathbf{R_f}$ = 0.31 (SiO_2, pentane/Et_2O 2:1); **Optical rotation**: $[\alpha]_D^{25}$ = +31.8 (*c* 0.565, $CHCl_3$); **FTIR (neat)**: $\tilde{\nu}$ = 2959, 1755, 1724, 1440, 1377, 1255, 1218, 1178, 1078, 1019, 991, 934, 882, 776, 738 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.04 – 6.02 (m, 1H), 5.97 (s, 1H), 5.15 (d, *J* = 4.5 Hz, 1H), 4.33 – 4.18 (m, 2H), 3.73 (s, 3H), 3.12 (dd, *J* = 14.4, 5.2 Hz, 1H), 2.46 – 2.37 (m, 2H), 2.18 – 2.09 (m, 1H), 1.97 (s, 3H), 1.90 (dd, *J* = 14.5, 0.8 Hz, 1H), 1.43 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 173.4, 169.0, 168.0, 142.8, 132.9, 97.6, 80.1, 71.2, 62.4, 57.6, 54.0, 52.1, 48.5, 39.3, 36.0, 21.1, 15.2, 14.1, 12.5; **HRMS (ESI)** m/z calcd. for $C_{19}H_{25}O_7ClNa$ $[M+Na]^+$: 423.1181, found: 423.1188; **X-ray crystal structure** is given in the appendices section.

Conversion of acetyl-furan 3.145 to chloro-furan 3.144



Acetyl-furan **3.145** (702 mg, 1.75 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (120 ml) and cooled to –78 °C. Triethylsilane (514 mg, 4.38 mmol, 2.5 eq) and boron trifluoride etherate (621 mg, 4.38 mmol, 2.5 eq) were added. The reaction mixture was stirred at –78 °C for 1 h and then allowed to warm to r.t. over a period of 12 h. The reaction mixture was cooled to 0 °C and water (80 ml) was slowly added. The mixture was extracted with Et_2O (3 x 80 ml) and the combined organic layers were washed with brine (50 ml), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, pentane/Et_2O 4:1) to afford the chloro-furan **3.144** (525 mg, 1.53 mmol, 88%) as a colorless solid.

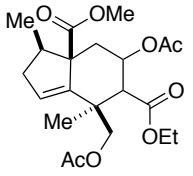
9-Ethyl 5a-methyl (1*R*,4*R*,5a*R*,6*R*,9*S*)-1,6-dimethyl-1,2,4,5,6,7-hexahydro-5a*H*-1,4-methanocyclopenta[*d*]oxepine-5a,9-dicarboxylate (3.148):



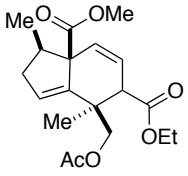
Chloro-furan **3.144** (483 mg, 1.41 mmol, 1.0 eq) was dissolved in benzene (35 ml). $Sn(Bu)_3H$ (487 mg, 1.62 mmol, 1.15 eq) and AIBN (23.9 mg, 0.14 mmol, 0.1 eq) were added and the

mixture was heated to 100 °C and stirred for 2 h. After cooling to r.t. volatiles were evaporated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, pentane/Et_2O 3:1) to afford hydro-furan **3.148** (411 mg, 1.34 mmol, 95%) as a colorless oil. $\mathbf{R_f}$ = 0.16 (SiO_2, pentane/Et_2O 3:1); **Optical rotation**: $[\alpha]_D^{27}$ = +9 (*c* 0.776, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 2955, 2880, 1725, 1450, 1378, 1337, 1196, 1155, 1049, 1023, 989, 925, 664, 627 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.72 (s, 1H), 4.56 (t, *J* = 5.2 Hz, 1H), 4.20 – 4.04 (m, 2H), 3.78 (d, *J* = 7.7 Hz, 1H), 3.69 (s, 3H), 3.46 (d, *J* = 7.7 Hz, 1H), 3.01 (dd, *J* = 14.2, 4.7 Hz, 1H), 2.83 (dd, *J* = 5.9, 1.1 Hz, 1H), 2.39 – 2.23 (m, 2H), 2.13 – 2.03 (m, 1H), 1.71 (d, *J* = 14.5 Hz, 1H), 1.35 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 174.3, 169.7, 145.8, 126.6, 77.4, 76.7, 60.3, 58.3, 55.7, 51.7, 48.9, 44.8, 39.0, 37.7, 17.4, 15.2, 14.4; **HRMS (ESI)** m/z calcd. for $C_{17}H_{25}O_5$ $[M+H]^+$: 309.1697, found: 309.1698.

6-Ethyl 3a-methyl (3*R*,3a*R*,6*S*,7*R*)-5-acetoxy-7-(acetoxymethyl)-3,7-dimethyl-2,3,4,5,6,7-hexahydro-3a*H*-indene-3a,6-dicarboxylate (3.149) and 6-Ethyl 3a-methyl (3*R*,3a*S*,7*R*)-7-(acetoxymethyl)-3,7-dimethyl-2,3,6,7-tetrahydro-3a*H*-indene-3a,6-dicarboxylate (3.150):



3.149



3.150

Hydro-furan **3.148** (44.7 mg, 145 µmol, 1.0 eq) was dissolved in Ac_2O (0.9 ml). The solution was cooled to –20 °C and boron trifluoride etherate (63.2 mg, 435 µmol, 3.0 eq) was added. The reaction was allowed to warm to r.t. over 12 h. The reaction mixture was cooled to 0 °C and water (1.0 ml) was added dropwise. The reaction mixture was stirred for 10 min and warmed to r.t. The mixture was extracted with Et_2O (3 x 1.5 ml), washed with brine (1.5 ml), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, pentane/Et_2O 2:1) to afford diacetylated compound **3.149** (35.4 mg, 87 µmol, 60%) as a yellow oil and monoacetylated compound **3.150** (31.7 mg, 46 µmol, 32%) as a colorless oil.

Diacetyl 3.149: $\mathbf{R_f}$ = 0.17 (SiO_2, pentane/Et_2O 2:1); **Optical rotation**: $[\alpha]_D^{27}$ = +8.9 (*c* 0.344, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3480, 2956, 1727, 1440, 1367, 1224, 1028, 908, 790, 664 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.83 (s, 1H), 5.30 – 5.23 (m, 1H), 4.19 – 4.03 (m, 2H), 3.77 (d, *J* = 11.3 Hz, 1H), 3.70 (d, *J* = 11.4 Hz, 1H), 3.65 (s, 3H), 3.13 (d, *J* = 5.4 Hz, 1H), 2.65 (dd, *J* = 12.3, 4.8 Hz, 1H), 2.51 – 2.36 (m, 2H), 2.26 – 2.14 (m, 1H), 2.07 (s, 3H), 2.03 – 1.97 (m, 1H), 1.99 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.15 (s, 3H), 0.94 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 174.3, 170.9, 170.8, 169.9, 143.3, 131.1, 68.8, 68.7, 60.3, 59.5, 51.8, 49.5, 49.1, 40.5, 39.1, 34.5, 21.5, 21.1, 21.0, 14.5; **HRMS (ESI)** m/z calcd. for $C_{21}H_{30}O_8Na$ $[M+Na]^+$: 433.1833, found: 433.1835.

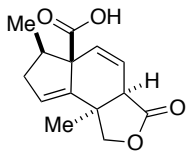
Monoacetyl 3.150: $\mathbf{R_f}$ = 0.32 (SiO_2, pentane/Et_2O 2:1); **Optical rotation**: $[\alpha]_D^{25}$ = +223.8 (*c* 0.141, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 2957, 1725, 1454, 1372, 1320, 1222, 1141, 1033, 793 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.22 (d, *J* = 10.0 Hz, 1H), 5.82 (s, 1H), 5.58 (dd, *J* = 10.0, 5.1 Hz, 1H), 4.14 – 4.01 (m, 2H), 3.92 (d, *J* = 10.9 Hz, 1H), 3.74 (d, *J* = 10.9 Hz, 1H), 3.65 (s, 3H), 3.15 (d, *J* = 5.1 Hz, 1H), 2.48 – 2.29 (m, 3H), 2.04 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.19 (s, 3H), 1.03 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 173.1, 171.3, 170.9, 143.2, 132.3, 129.8, 122.1, 68.3, 60.8, 59.3, 51.8, 50.2, 47.9, 39.7, 38.8, 21.0, 19.4, 14.4, 14.3. **HRMS (ESI)** m/z calcd. for $C_{19}H_{27}O_6$ $[M+H]^+$: 351.1802, found: 351.1800.

Methyl (3a*R*,5a*S*,6*R*,8b*R*)-6,8b-dimethyl-3-oxo-1,3,3a,6,7,8b-hexahydro-5a*H*-indeno[4,5-*c*]furan-5a-carboxylate (3.164):

Monoacetate **3.150** (36.8 mg, 105 µmol, 1.0 eq) was dissolved in MeOH (7.5 ml). K_2CO_3 (104 mg, 735 µmol, 7.0 eq) was added and the reaction mixture was stirred at r.t. for 18 h. The slightly yellow solution was diluted with EtOAc (15 ml) and aq. HCl (1 M, 10 ml) was added. The aq. layer was extracted with EtOAc (3 x 15 ml), the combined organic layers were washed with brine (10 ml), dried over Na_2SO_4,

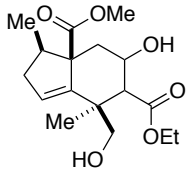
filtered and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, pentane/EtOAc 3:1) to afford lactone **3.164** (10 mg, 39 µmol, 37%) as a white solid. **M.p.**: 134.1 – 134.5 °C; **R_f** = 0.30 (SiO_2, pentane/Et_2O 2:1); **Optical rotation**: $[\alpha]_D^{25}$ = –43.6 (*c* 0.195, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 2969, 2922, 1763, 1720, 1436, 1233, 1218, 1167, 1067, 1001, 897, 836, 797, 741, 705, 667 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.17 (ddd, *J* = 9.9, 2.7, 0.8 Hz, 1H), 5.98 (d, *J* = 3.0 Hz, 1H), 5.60 (dd, *J* = 10.0, 3.2 Hz, 1H), 3.94 (d, *J* = 9.2 Hz, 1H), 3.85 (d, *J* = 9.2 Hz, 1H), 3.70 (s, 3H), 2.81 (t, *J* = 3.0 Hz, 1H), 2.50 – 2.36 (m, 1H), 2.34 – 2.22 (m, 2H), 1.41 (s, 3H), 1.05 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 176.0, 173.3, 142.1, 132.2, 130.9, 119.9, 74.3, 58.7, 52.2, 52.1, 47.9, 41.4, 38.8, 23.4, 14.5; **HRMS (ESI)** m/z calcd. for $C_{15}H_{19}O_4$ $[M+H]^+$: 263.1278, found: 263.1275; **X-ray crystal structure** is given in the appendices section.

(3a*R*,5a*S*,6*R*,8b*R*)-6,8b-Dimethyl-3-oxo-1,3,3a,6,7,8b-hexahydro-5a*H*-indeno[4,5-*c*]furan-5a-carboxylic acid (3.173):



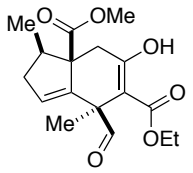
Monoacetate **3.150** (30.0 mg, 58.0 µmol, 1.0 eq) was dissolved in ^{i}PrOH (5.0 ml) at r.t. NaOH (34 mg, 86.2 µmol, 10 eq) was added and the solution was stirred for 16 h. Aq. HCl (3 M, 3.0 ml) was added and the aq. layer was extracted with EtOAc (5 x 5.0 ml). The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, pentane/EtOAc 1:4) to afford carboxylic acid **3.173** (17.3 mg, 85.6 µmol, 81%) as a colorless oil. **R_f** = 0.27 (SiO_2, pentane/EtOAc 1:4); **Optical rotation**: $[\alpha]_D^{26}$ = –65.7 (*c* 0.427, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 2964, 2929, 2851, 2361, 1768, 1728, 1467, 1381, 1234, 1167, 1114, 1029, 1015, 897, 808, 755, 671 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.15 (dd, *J* = 10.0, 2.7 Hz, 1H), 6.01 (d, *J* = 2.7 Hz, 1H), 5.64 (dd, *J* = 10.0, 3.2 Hz, 1H), 4.08 (d, *J* = 9.2 Hz, 1H), 3.90 (d, *J* = 9.3 Hz, 1H), 2.84 (t, *J* = 2.9 Hz, 1H), 2.49 – 2.41 (m, 1H), 2.38 – 2.28 (m, 2H), 1.43 (s, 3H), 1.15 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 178.0, 175.9, 141.9, 131.6, 131.4, 120.5, 74.3, 58.4, 52.2, 48.0, 41.5, 38.8, 23.4, 14.5; **HRMS (ESI)** m/z calcd. for $C_{14}H_{17}O_4$ $[M+H]^+$: 249.1121, found: 249.1118.

6-Ethyl 3a-methyl (3*R*,3a*R*,6*S*,7*R*)-5-hydroxy-7-(hydroxymethyl)-3,7-dimethyl-2,3,4,5,6,7-hexahydro-3a*H*-indene-3a,6-dicarboxylate (3.152):



Diacetyl **3.149** (38.7 mg, 94.3 µmol, 1.0 eq) was dissolved in MeOH (1.5 ml), K_2CO_3 (53.6 mg, 38.4 µmol, 4.0 eq) was added and the reaction mixture was stirred at r.t. for 16 h. The reaction mixture was diluted with EtOAc (5 ml), aq. HCl (1 M, 2.0 ml) was added and the mixture was extracted with EtOAc (3 x 2.0 ml). The combined organic layers were washed with brine (1.5 ml), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, pentane/EtOAc 1:1) to afford the diol **3.152** (30.1 mg, 92.4 µmol, 98%) as a colorless sticky oil. $\mathbf{R_f}$ = 0.45 (SiO_2, pentane/EtOAc 1:1); **Optical rotation**: $[\alpha]_D^{25}$ = –1.9 (*c* 0.254, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3448, 2954, 1721, 1448, 1178, 1027, 885, 780, 710, 660 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.86 (s, 1H), 4.20 – 4.05 (m, 3H), 3.70 (s, 3H), 3.20 (d, *J* = 11.3 Hz, 1H), 3.07 (d, *J* = 11.3 Hz, 1H), 2.67 – 2.62 (m, 2H), 2.50 – 2.39 (m, 2H), 2.16 – 2.02 (m, 4H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.17 (s, 3H), 0.96 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 175.4, 171.5, 142.5, 132.8, 66.6, 66.3, 60.4, 59.9, 54.3, 52.2, 48.6, 43.0, 39.0, 37.8, 21.4, 14.7, 14.4; **HRMS (ESI)** m/z calcd. for $C_{17}H_{26}O_6Na$ $[M+Na]^+$: 349.1622, found: 349.1626.

6-Ethyl 3a-methyl (3*R*,3a*R*,7*S*)-7-formyl-5-hydroxy-3,7-dimethyl-2,3,4,7-tetrahydro-3a*H*-indene-3a,6-dicarboxylate (3.153):



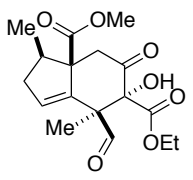
Dimethyl sulfide (17.2 mg, 20 µmol, 4.3 eq) was dissolved in CH_2Cl_2 (1.0 ml) and NCS (34.0 mg, 0.26 mmol, 4.0 eq) was added. The solution was cooled to –78 °C and stirred for 1 h. A solution of diol **3.152** (21.0 mg, 64.0 µmol, 1.0 eq) in CH_2Cl_2 (1.0 ml) was added to white suspension. The reaction mixture was stirred for 1 h at –78 °C, then a solution of triethylamine (36 µL, 0.25 mmol, 4.0 eq) in CH_2Cl_2 (0.5 ml) was added and the mixture was warmed to r.t., aq. HCl (1 M, 1.0 ml) was added and the aq. layer was extracted with CH_2Cl_2 (3 x 1.5 ml). The combined organic layers were washed with brine (1 ml), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude was

purified by flash column chromatography (SiO_2, pentane/Et_2O 3:1) to afford the enol **3.153** (15 mg, 46 µmol, 72%) as a colorless oil. $\mathbf{R_f}$ = 0.39 (SiO_2, pentane/Et_2O 3:1); **Optical rotation**: $[\alpha]_D^{25}$ = –124.9 (*c* 0.611, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 2960, 2934, 2848, 1728, 1642, 1607, 1458, 1402, 1297, 1228, 1076, 863, 732, 631 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 12.94 (s, 1H), 9.13 (s, 1H), 5.98 (s, 1H), 4.27 – 4.12 (m, 2H), 3.63 (s, 3H), 3.25 (d, *J* = 16.4 Hz, 1H), 2.54 (ddd, *J* = 15.3, 7.3, 3.1 Hz, 1H), 2.37 – 2.19 (m, 2H), 2.16 (d, *J* = 16.3 Hz, 1H), 1.47 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 197.3, 175.8, 172.8, 171.5, 141.3, 133.3, 99.0, 61.1, 60.2, 51.9, 50.8, 46.4, 39.8, 38.9, 22.7, 15.0, 14.1; **HRMS (ESI)** m/z calcd. for $C_{17}H_{23}O_6$ $[M+H]^+$: 323.1489, found: 323.1490.

Alternative procedure for the synthesis of enol 3.153:

To a flask charged with flame-dried molecular sieves (4 Å, 120 mg) was added a solution of diol **3.152** (58.1 mg, 178 µmol, 1.0 eq) in CH_2Cl_2 (5 ml). NMO (56.0 mg, 463 µmol, 2.6 eq) was added at r.t. and the reaction mixture was stirred for 20 min. TPAP (12.9 mg, 35 µmol, 0.2 eq) was added and the solution was stirred at r.t. for 24 h, during which the color turned from green to dark blue. The reaction mixture was filtered over Celite and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, pentane/Et_2O 3:1) to yield enol **3.153** (39.0 mg, 121 µmol, 68%) as a colorless oil.

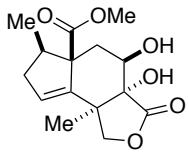
6-Ethyl 3a-methyl (3*R*,3a*R*,7*S*)-7-formyl-6-hydroxy-3,7-dimethyl-5-oxo-2,3,4,5,6,7-hexa-hydro-3a*H*-indene-3a,6-dicarboxylate (3.154):



Enol **3.153** (89.0 mg, 276 µmol, 1.0 eq) was dissolved in ^{i}PrOH (5.0 ml) and the solution degassed (thaw freeze method, 2 cycles) and the atmosphere refilled with oxygen. $CeCl_3 \cdot 7\ H_2O$ (105 mg, 276 µmol, 1.0 eq) was added at r.t. and oxygen was bubbled through the colorless solution for 15 min. The solution was stirred under oxygen atmosphere at r.t. for 20 h. Water (5.0 ml) was added, the mixture was extracted with EtOAc (3 x 5.0 ml), the combined

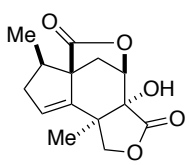
organic layers were washed with brine (3.0 ml), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography (SiO_2, pentane/Et_2O 2:1) to afford α-hydroxylated product **3.154** (40.3 mg, 119 µmol, 43%) as a colorless oil. $\mathbf{R_f}$ = 0.37 (SiO_2, pentane/Et_2O 1:1); **Optical rotation**: $[\alpha]_D^{25}$ = –68.8 (*c* 0.527, $CHCl_3$); **FTIR (neat)**: $\tilde{\nu}$ = 3454, 2959, 1724, 1453, 1373, 1217, 1162, 1099, 1001, 916, 859, 732, 653 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.40 (s, 1H), 6.11 (s, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.91 (s, 1H), 3.64 (s, 3H), 3.51 (d, *J* = 14.7 Hz, 1H), 2.84 (d, *J* = 14.7 Hz, 1H), 2.59 – 2.45 (m, 2H), 2.32 – 2.20 (m, 1H), 1.40 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 202.8, 197.3, 172.5, 170.4, 138.8, 135.1, 82.9, 63.8, 61.1, 58.7, 52.2, 50.6, 44.4, 39.3, 14.6, 14.5, 14.1; **HRMS (ESI)** m/z calcd. for $C_{17}H_{23}O_7$ $[M+H]^+$: 339.1438, found: 339.1441.

Methyl (3a*R*,5a*R*,6*R*,8b*R*)-3a,4-dihydroxy-6,8b-dimethyl-3-oxo-1,3,3a,4,5,6,7,8b-octahydro-5a*H*-indeno[4,5-*c*]furan-5a-carboxylate (3.160):



α-Hydroxyester **3.154** (3.35 mg, 9.90 µmol, 1.0 eq) was dissolved in MeOH (0.2 ml) and cooled to 0 °C. $NaBH_4$ (1.87 mg, 49.5 µmol, 5.0 eq) was added in small portions and the reaction mixture was allowed to warm to r.t. over 12 h. The reaction mixture was cooled to 0 °C and water (1.5 ml) was added. The aq. layer was extracted with EtOAc (4 x 1.5 ml) and the combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to afford crude diol **3.160** as colorless solid. The diol **3.160** was used without further purification. $\mathbf{R_f}$ = 0.11 (SiO_2, pentane/EtOAc 3:1); **HRMS (ESI)** m/z calcd. for $C_{15}H_{20}O_6$ $[M+Na]^+$: 319.1152, found: 319.1153.

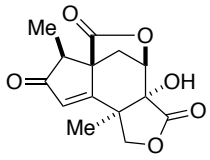
(3a*R*,4*R*,6a*R*,7*R*,9b*R*)-3a-Hydroxy-7,9b-dimethyl-1,3a,4,7,8,9b-hexahydro-3*H*,6*H*-4,6a-methanocyclopenta[*c*]furo[3,4-*e*]oxepine-3,6-dione (3.161):



Diol **3.160** (6.0 mg, 20 µmol, 1.0 eq) was dissolved in toluene (0.4 ml) and *p*-toluenesulfonic acid monohydrate (0.8 mg, 4 µmol, 0.2 eq) was added. The reaction mixture was stirred at

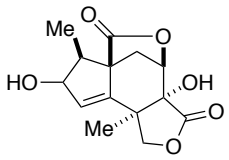
70 °C for 2 h. The reaction mixture was diluted with EtOAc (3 ml) and washed with aq. sat. $NaHCO_3$ (2 ml). The aq. layer was extracted with EtOAc (3 x 1.5 ml), the combined organic layer was washed with brine (1.5 ml), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, pentane/EtOAc 3:1) to afford dilactone **3.161** (0.7 mg, 2.6 µmol, 27%, over two steps) as a white solid. **M.p.**: 129.5 – 130.2 °C; $\mathbf{R_f}$ = 0.53 (SiO_2, pentane/EtOAc 2:1); **Optical rotation**: $[\alpha]_D^{25}$ = +56.7 (*c* 0.21, $CHCl_3$); **FTIR (neat)**: $\tilde{\nu}$ = 3448, 2921, 2851, 1782, 1753, 1457, 1376, 1326, 1221, 1185, 1113, 1016, 1000, 938, 818, 732, 639 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.87 (s, 1H), 4.63 (d, *J* = 5.9 Hz, 1H), 3.98 (q, *J* = 9.5 Hz, 2H), 2.58 (ddd, *J* = 15.6, 8.1, 2.9 Hz, 1H), 2.48 (dd, *J* = 11.9, 5.9 Hz, 1H), 2.44 – 2.37 (m, 1H), 2.32 (ddd, *J* = 15.5, 9.7, 1.9 Hz, 1H), 2.21 (d, *J* = 12.1 Hz, 1H), 1.36 (s, 3H), 1.32 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 177.7, 174.9, 140.6, 129.8, 78.9, 78.0, 74.4, 56.6, 43.3, 39.2, 37.0, 35.0, 21.4, 13.3; **HRMS (ESI)** m/z calcd. for $C_{14}H_{16}O_5Na$ $[M+Na]^+$: 287.0890, found: 287.0894.

(3a*R*,4*R*,6a*R*,7*S*,9b*R*)-3a-Hydroxy-7,9b-dimethyl-1,3a,4,9b-tetrahydro-3*H*,6*H*-4,6a-methanocyclopenta[*c*]furo[3,4-*e*]oxepine-3,6,8(7*H*)-trione (3.162):



CrO_3 (21.0 mg, 0.21 mmol, 15.0 eq) was dissolved in CH_2Cl_2 (3.0 ml) and 3,5-dimethylpyrazole (20.4 mg, 0.21 mmol, 15 eq) was added. The reaction mixture was stirred for 30 min at r.t. and the color turned to dark red. A solution of dilactone **3.161** (3.7 mg, 14 µmol, 1.0 eq) in CH_2Cl_2 (1 ml) was added and the solution was stirred at r.t. for 48 h. Celite was added and the reaction was stirred for 16 h. The reaction mixture was filtered over Celite and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (pentane/EtOAc 1:1) to afford enone **3.162** (yield not determined due to low amount and impurity). $\mathbf{R_f}$ = 0.33 (pentane/EtOAc 1:1); **^{1}H NMR** (250 MHz, $CDCl_3$) δ = 6.29 (s, 1H), 4.82 (s, 1H), 4.16 – 4.03 (m, 3H), 2.75 – 2.48 (m, 3H), 1.52 (s, 3H), 1.41 (d, *J* = 7.4 Hz, 3H); **(ESI)** m/z calcd. for $C_{28}H_{27}O_{12}$ $[2M-H]^-$: 555.15, found: 555.1

(3a*R*,4*R*,6a*R*,7*S*,9b*R*)-3a,8-Dihydroxy-7,9b-dimethyl-1,3a,4,7,8,9b-hexahydro-3*H*,6*H*-4,6a-methanocyclopenta[*c*]furo[3,4-*e*]oxepine-3,6-dione (3.163)



Enone **3.162** (1.0 mg, 3.6 µmol, 1.0 eq) was dissolved in MeOH/THF (0.4 ml, 1:3) and $CeCl_3 \cdot 7\,H_2O$ (12.1 mg, 32.4 µmol, 9.0 eq) was added. The reaction mixture was stirred for 10 min and then cooled to –78 °C. $NaBH_4$ (1.2 mg, 32.4 µmol, 9.0 eq) was added in small portions and the reaction mixture was stirred at –78 °C for 2 h. The cooling bath was removed and the reaction mixture was stirred at r.t. for 12 h. Brine (1.0 ml) was added and the aq. layer was extracted with EtOAc (5 x 2 ml). The combined organic layers were washed with brine (1.5 ml), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, pentane/EtOAc 1:4) to afford allylic alcohol **3.163** (yield not determined due to low amount) as a single diastereomer. $\mathbf{R_f}$ = 0.48 (SiO_2, pentane/EtOAc 1:4); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.90 (d, *J* = 1.0 Hz, 1H), 4.79 (dd, *J* = 7.7, 1.6 Hz, 1H), 4.66 (d, *J* = 5.9 Hz, 1H), 4.00 (d, *J* = 9.5 Hz, 1H), 3.91 (dd, *J* = 9.5, 0.9 Hz, 1H), 2.48 (dd, *J* = 12.5, 6.2 Hz, 1H), 2.31 (d, *J* = 12.2 Hz, 1H), 2.16 – 2.08 (m, 1H), 1.40 (d, *J* = 0.8 Hz, 3H), 1.37 (d, *J* = 7.2 Hz, 3H); **HRMS (ESI)** m/z calcd. for $C_{14}H_{16}O_6Na$ $[M+Na]^+$: 303.0839, found: 303.0838.

7.4 Preparation of Antimalarial Endoperoxides

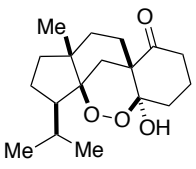
Synthesis of allylic alcohol **4.52** was performed according to the reported procedure with the exception of ketoaldehyde **4.51**.[277]

Generel procedure for the endoperoxide synthesis:

Method A: Diketone **4.55** (64.0 µmol, 1.0 eq) was allowed to react in an open-flask (or dissolved in EtOAc) exposed to sunlight and air. After 16 h, the yellow solid was dissolved in EtOAc and purified by flash column chromatography (SiO_2, pentane/EtOAc 12:1) to give the endoperoxides **4.48** and **4.49** as white solids.

Method B: Diketone **4.55** (13.2 µmol, 1.0 eq) was dissolved in AcOH (0.36 ml), $Mn(OAc)_3$ (1.99 µmol, 0.15 eq) was added, and the reaction flask was charged with a balloon containing O_2. The yellow solution was stirred at r.t. for 19 h and then quenched with H_2O (0.2 ml) and sat. aq. $NaHCO_3$ solution (0.8 ml). The aqueous phase was extracted with EtOAc (4 x 1 ml) and the combined organic layers were washed with sat. aq. $NaHCO_3$ solution (1 ml) and brine (0.5 ml), then dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (SiO_2) to obtain the endoperoxides **4.48** and **4.49** as white solids.

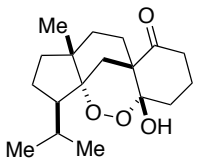
(3*R*,3*aS*,5*aR*,9*aR*,11*aR*)-5*a*-Hydroxy-3-isopropyl-11*a*-methyloctahydro-1*H*-3*a*,9*a*-methanobenzo[*c*]cyclopenta[*g*][1,2]dioxocin-9(10*H*)-one (4.48):



White solid (3.16 mg, 10.2 µmol, 77%); $\mathbf{R_f}$ = 0.63 (SiO_2, pentane/EtOAc 4:1); **M.p.:** 124.6 – 126.4 °C; **Optical rotation**: $[\alpha]_D^{25}$ = –116.0 (*c* 0.236, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3452, 3395, 2952, 2927, 2867, 1696, 1470, 1260, 1179, 1163, 1068, 1012, 991, 891, 762 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.14 (s, 1H), 2.63 – 2.54 (m, 1H), 2.33 – 2.27 (m, 1H), 2.16 (d, *J* = 13.5 Hz, 1H), 2.08 – 2.01 (m, 3H), 1.93 – 1.89 (m, 1H), 1.76 – 1.72 (m, 2H), 1.70 – 1.66 (m, 2H), 1.65 – 1.64 (m, 2H), 1.57 – 1.50 (m, 5H), 1.19 (s, 3H), 1.04 (d, *J* = 6.4 Hz,

3H), 0.85 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* = 211.1, 103.4, 90.5, 60.5, 50.6, 45.7, 40.2, 35.8, 34.5, 30.8, 28.7, 28.5, 28.4, 27.3, 23.8, 22.2, 22.0, 19.4; **HRMS (ESI)** m/z calcd for $C_{18}H_{28}O_4Na$ $[M+Na]^+$: 331.1880, found 331.1881.

(3*R*,3*aR*,5*aS*,9*aS*,11*aR*)-5*a*-Hydroxy-3-isopropyl-11*a*-methyloctahydro 1*H*-3*a*,9*a*-methanobenzo[*c*]cyclopenta[*g*][1,2]dioxocin-9(10*H*)-one (4.49):



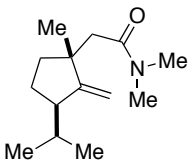
White solid (0.79 mg, 2.56 µmol, 19%); **R_f** = 0.50 (SiO_2, pentane/EtOAc 4:1); **M.p.:** 147.5 – 149.1 °C; **Optical rotation**: $[\alpha]_D^{25}$ = +118.2 (*c* 0.045, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3501, 3428, 2965, 2923, 1456, 1377, 1313, 1261, 1250, 1160, 1068, 1160, 1068, 999, 961, 885, 799, 785, 619 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* = 3.23 (s, 1H), 2.73 – 2.57 (m, 2H), 2.43 (dd, *J* = 13.9, 2.1 Hz, 1H), 2.32 (dd, *J* = 15.7, 4.0 Hz, 1H), 2.15 – 2.10 (m, 1H), 2.03 (d, *J* = 13.8 Hz, 1H), 1.99 – 1.96 (m, 1H), 1.89 – 1.81 (m, 2H), 1.76 – 1.70 (m, 1H), 1.68 – 1.63 (m, 2H), 1.59 – 1.55 (m, 2H), 1.47 – 1.38 (m, 2H), 1.34 – 1.25 (m, 2H), 1.06 (d, *J* = 6.3 Hz, 3H), 0.96 (s, 3H), 0.89 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* = 211.0, 103.4, 98.0, 52.8, 52.1, 45.9, 36.2, 35.7, 33.0, 30.5, 29.1, 28.4, 26.7, 24.9, 24.6, 23.4, 22.2, 19.6; **HRMS (ESI)** m/z calcd for $C_{18}H_{28}O_4Na$ $[M+Na]^+$: 331.1880, found 331.1880; **X-ray crystal structure** is given in the appendices section.

(*S*)-3-Isopropyl-6-oxoheptanal (4.51):

The olefin[277] (1.85 g, 13.4 mmol, 1.0 eq) was dissolved in MeOH (7.0 ml) and CH_2Cl_2 (35.0 ml). The colorless solution was cooled to −78 °C and ozone was bubbled through the solution until it turned blue. The reaction was stirred for additional 5 min at −78 °C and oxygen was bubbled through the blue solution until the color disappeared. Zn (1.75 g, 26.8 mmol, 2.0 eq) and AcOH (2.30 ml, 2.41 g, 40.1 mmol, 3.0 eq) were added at −78 °C and the mixture was allowed to warm to r.t. for 1 h and stirred for additional 15 min at this temperature. The suspension was filtered over Celite and the filter cake washed with CH_2Cl_2 (3 x 15 ml). The organic layer was extracted with

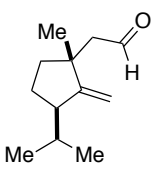
sat. $NaHCO_3$ solution (15 ml) and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 ml). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to obtain pale yellow oil. The residue was purified by flash chromatography (SiO_2, pentane/Et_2O 4:1) to yield the ketoaldehyde **4.51** as pale yellow oil (1.85 g, 10.8 mmol, 81%). The analytical data were in good agreement as previously reported.[277]

2-((1*R*,3*R*)-3-Isopropyl-1-methyl-2-methylenecyclopentyl)-*N*,*N*-dimethylacetamide (4.53):



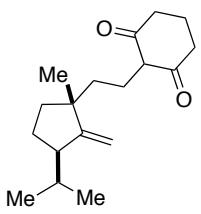
The allyl alcohol **4.52** (18 mg, 0.12 mmol, 1.0 eq) was dissolved in *p*-xylene (1.0 ml) and 1,1-dimethoxyethyl(dimethyl)amine (90% in MeOH, 173 mg, 1.17 mmol, 10 eq) was added. Argon was bubbled for 2 minutes through the yellow solution, and the reaction vessel was then sealed and heated to 150 °C behind a blast shield. After 16 h, the mixture was allowed to cool to r.t. and then completely evaporated to obtain an orange oil. The residue was purified by flash chromatography (SiO_2, pentane/EtOAc 4:1 to 3:1) to yield the amide **4.53** (24.8 mg, 0.11 mmol, 95%, d.r. 24:1) as a slightly yellow oil. $\mathbf{R_f}$ = 0.08 (SiO_2, pentane/Et_2O 4:1); **Optical rotation**: $[\alpha]_D^{25}$ = +23.1 (*c* 0.074, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 2955, 2870, 1642, 1466, 1394, 1264, 1126, 882 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.80 (d, *J* = 2.9 Hz, 1H), 4.77 (d, *J* = 2.5 Hz, 1H), 3.00 (s, 3H), 2.92 (s, 3H), 2.59 – 2.52 (m, 1H), 2.53 (d, *J* = 15.1, Hz, 1H), 2.37 (d, *J* = 15.1, 1H), 2.01 – 1.93 (m, 1H), 1.87 – 1.79 (m, 1H), 1.67 – 1.59 (m, 2H), 1.45 – 1.35 (m, 1H), 1.09 (s, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.77 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 171.8, 163.4, 103.3, 50.9, 45.2, 43.8, 38.0, 37.5, 35.5, 28.9, 27.6, 23.3, 22.0, 16.6; **HRMS (ESI)** m/z calcd for $C_{14}H_{26}NO$ $[M+H]^+$: 224.2009, found 224.2015.

2-((1*R*,3*R*)-3-Isopropyl-1-methyl-2-methylenecyclopentyl)acetaldehyde (4.54):



The amide **4.53** (4.3 mg, 19.3 µmol, 1.0 eq) was dissolved in dry THF (0.2 ml), 1,1,3,3-tetramethyldisiloxane (8.01 mg, 10 µl, 57.9 µmol, 3.0 eq) and titanium(IV)isopropoxide (16.7 mg, 20 µl, 57.9 µmol, 3.0 eq) were added, and the reaction mixture was stirred at r.t. for 18 h. Et_2O (1.0 ml) was added, the mixture was washed with aq. HCl (1 M, 3 x 0.3 ml), and the combined aqueous layers were re-extracted with Et_2O (3 x 0.5 ml). The combined organic layers were washed with brine (0.5 ml), dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (SiO_2, pentane/Et_2O 4:1) to yield the aldehyde **4.54** (3.3 mg, 18.3 µmol, 95%) as a colorless oil. The analytical data were in good agreement as previously reported.[277]

2-(2-((1*R*,3*R*)-3-Isopropyl-1-methyl-2-methylenecyclopentyl)ethyl)-cyclohexane-1,3-dione (4.55):



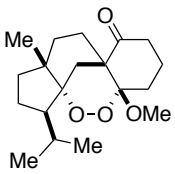
Aldehyde **4.54** (5.68 g, 31.5 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (300 ml). Cyclohexan-1,3-dione (10.8 g, 94.4 mmol, 3.0 eq), Hantzsch ester (16.3 g, 63.0 mmol, 2.0 eq) and L-proline (370 mg, 3.15 mmol, 0.1 eq) were added. The yellow mixture was stirred at room temperature for 19 h and was subsequently washed with water (20 ml), aq. HCl (10%, 3 x 15 ml) and brine (15 ml). The combined aqueous layer was extracted with CH_2Cl_2 (20 ml) and the combined organic layers were dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2, pentane/EtOAc 4:1 to 1:1) to yield the diketone **4.55** (7.92 g, 28.7 mmol, 91%) as an instable yellow solid. **HRMS (ESI)** m/z calcd for $C_{18}H_{29}O_2$ $[M+H]^+$: 277.2162, found 277.2162.

General method for Ag_2O mediated *O*-alkylation of endoperoxides:

To a solution of endoperoxide (**4.48** or **4.49**) (3.74 µmol, 1.0 eq) in MeCN (0.10 ml), MeI (131 µmol, 35 eq) and Ag_2O (14.2 µmol, 3.8 eq) were added, and the reaction mixture was stirred at 40 °C for 16 h. The mixture was

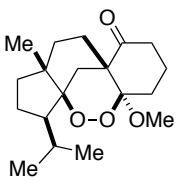
allowed to cool to r.t. and was then filtered over Celite and rinsed with EtOAc (3 x 0.3 ml). The solvent was removed *in vacuo* and the yellow solid was purified by flash column chromatography (SiO_2) to yield the corresponding methylated endoperoxides **4.61** and **4.62**.

(3*R*,3*aR*,5*aS*,9*aS*,11*aR*)-3-Isopropyl-5*a*-methoxy-11*a*-methyloctahydro-1*H*-3*a*,9*a*-methanobenzo[*c*]cyclopenta[*g*][1,2]dioxocin-9(10*H*)-one (4.61):



Flash column chromatography (SiO_2, pentane/Et_2O 10:1); white solid (5.22 mg, 16.0 μmol, 88%); $\mathbf{R_f}$ = 0.55 (pentane/Et_2O 3:1); **M.p.:** 136.6 – 137.9 °C; **Optical rotation**: $[\alpha]_D^{25}$ = +98.1 (*c* 0.058, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 2954, 2924, 2863, 1711, 1460, 1263, 1181, 1092, 1066, 1035, 928, 784 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.24 (s, 3H), 2.71 – 2.53 (m, 3H), 2.31 – 2.26 (m, 1H), 2.14 – 2.08 (m, 1H), 1.92 – 1.79 (m, 5H), 1.78 – 1.67 (m, 2H), 1.66 – 1.61 (m, 1H), 1.60 – 1.53 (m, 2H), 1.45 – 1.35 (m, 2H), 1.30 – 1.23 (m, 1H), 1.05 (d, *J* = 6.3 Hz, 3H), 0.94 (s, 3H), 0.87 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 211.1, 105.3, 97.5, 52.9, 51.9, 47.7, 45.9, 36.1, 35.8, 32.9, 30.4, 29.1, 26.7, 24.6, 23.9, 23.3, 22.3, 22.2, 19.3; **HRMS (ESI)** m/z calcd for $C_{19}H_{30}O_4Na$ $[M+Na]^+$: 345.2036, found 345.2040; **X-ray crystal structure** is given in the appendices section.

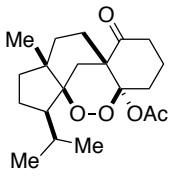
(3*R*,3*aS*,5*aR*,9*aR*,11*aR*)-3-Isopropyl-5*a*-methoxy-11*a*-methyloctahydro-1*H*-3*a*,9*a*-methanobenzo[*c*]cyclopenta[*g*][1,2]dioxocin-9(10*H*)-one (4.62):



Flash column chromatography (SiO_2, pentane/Et_2O 12:1); white solid (10.8 mg, 33.0 μmol, 54%); $\mathbf{R_f}$ = 0.59 (pentane/Et_2O 5:1); **M.p.:** 84.7 – 85.9 °C; **Optical rotation**: $[\alpha]_D^{25}$ = –59.5 (*c* 0.043, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 2954, 2869, 1707, 1455, 1378, 1316, 1262, 1200, 1060, 1031, 993, 899, 662, 628 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.32 (s, 3H), 2.65 – 2.49 (m, 2H), 2.39 – 2.33 (m, 1H), 2.21 – 2.13 (m, 2H), 2.03 – 1.96 (m, 1H), 1.93 – 1.86 (m, 2H), 1.84 – 1.75 (m, 2H), 1.67 – 1.58 (m, 4H), 1.55 – 1.48 (m, 1H), 1.46 – 1.40 (m, 2H), 1.37 – 1.32 (m, 1H), 1.13 (s, 3H), 1.03 (d, *J* = 6.3 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 211.7, 106.7, 89.1, 57.4, 53.8, 49.8, 45.4, 42.4, 37.7, 36.8,

34.2, 29.3, 27.2, 24.1, 24.0, 22.5, 21.8, 21.5, 18.5; **HRMS (ESI)** m/z calcd for $C_{19}H_{30}O_4Na$ $[M+Na]^+$: 345.2036, found 345.2041; **X-ray crystal structure** is given in the appendices section.

(3*R*,3*aS*,5*aR*,9*aR*,11*aR*)-3-Isopropyl-11*a*-methyl-9-oxodecahydro-1*H*-3*a*,9*a*-methanobenzo[*c*]cyclopenta[*g*][1,2]dioxocin-5*a*-yl acetate (4.63):



A solution of endoperoxide **4.48** (4.47 mg, 14.5 µmol, 1.0 eq) in CH_2Cl_2 (0.32 ml) was cooled to 0 °C. DMAP (1.08 mg, 8.7 µmol, 0.6 eq), 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (Barton's Base, 0.06 ml, 0.29 mmol, 20 eq) and Ac_2O (28.0 µl, 0.29 mmol, 20 eq) were added. The mixture was warmed to r.t. and stirred for 18 h. Et_2O (1 ml) was added and washed with aq. HCl (1 M, 2 x 0.3 ml) and sat. aq. $NaHCO_3$ solution (0.3 ml) and brine (0.3 ml). The organic layer was dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (pentane/Et_2O 6:1 to 4:1) to obtain the acetylated endoperoxide **4.63** as colorless sticky oil (3.88 mg, 11.1 µmol, 76%). $\mathbf{R_f}$ = 0.53 (SiO_2, pentane/Et_2O 2:1); **Optical rotation**: $[\alpha]_D^{25}$ = –13.9 (*c* 0.15, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 2951, 2927, 2869, 1762, 1709, 1459, 1369, 1259, 1209, 1170, 1013, 961, 630 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 2.82 (dt, *J* = 14.7, 4.6 Hz, 1H), 2.59 – 2.42 (m, 3H), 2.17 – 2.10 (m, 1H), 2.07 (s, 3H), 2.04 – 1.93 (m, 3H), 1.88 – 1.81 (m, 1H), 1.77 – 1.70 (m, 1H), 1.68 – 1.65 (m, 2H), 1.62 – 1.58 (m, 2H), 1.55 – 1.51 (m, 1H), 1.46 – 1.40 (m, 2H), 1.38 – 1.33 (m, 1H), 1.06 (s, 3H), 1.03 (d, *J* = 6.4 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 210.2, 168.8, 110.9, 90.2, 57.0, 53.3, 45.1, 40.0, 38.3, 36.6, 34.6, 28.8, 27.5, 26.6, 23.8, 21.9, 21.6, 21.5, 20.9, 18.6; **HRMS (ESI)** m/z calcd for $C_{20}H_{30}O_5Na$ $[M+Na]^+$: 373.1985, found 373.1992.

In Vitro Assay's were performed by the Swiss Tropical and Health Institute (Basel)

Activity against *P. falciparum*: In vitro activity against erythrocytic stages of *P. falciparum* was determined using a ^{3}H-hypoxanthine incorporation assay,[405, 406] using the drug-sensitive NF54 strain (Schipol Airport, The Netherlands)[407] and the standard drugs chloroquine (Sigma C6628) and artemisinin (Sigma 361593). Compounds were dissolved in DMSO at 10 mg/ml and added to parasite cultures incubated in RPMI 1640 medium without hypoxanthine, supplemented with HEPES (5.94 g/l), $NaHCO_3$ (2.1 g/l), neomycin (100 U/ml), Albumax (5 g/l) and washed human red cells A+ at 2.5% haematocrit (0.3% parasitaemia). Serial drug dilutions of eleven 3-fold dilution steps covering a range from 100 to 0.002 µg/ml were prepared. The 96-well plates were incubated in a humidified atmosphere at 37 °C, 4% CO_2, 3% O_2, 93% N_2. After 48 h 50 µl of ^{3}H-hypoxanthine (=0.5 µCi) was added to each well of the plate. The plates were incubated for a further 24 h under the same conditions. The plates were then harvested with a Betaplate™ cell harvester (Wallac, Zurich, Switzerland), and the red blood cells transferred onto a glass fibre filter and then washed with distilled water. The dried filters were inserted into a plastic foil with 10 ml of scintillation fluid, and counted in a Betaplate™ liquid scintillation counter (Wallac, Zurich, Switzerland). IC_{50} values were calculated from sigmoidal inhibition curves by linear regression using Microsoft Excel.[408]

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[407] T. Ponnudurai, A. D. Leeuwenberg, J. H. Meuwissen, *Trop. Geogr. Med.* **1981**, *33*, 50.

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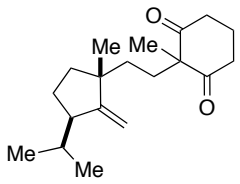
In vitro cytotoxicity with L-6 cells: Assays were performed in 96-well microtiter plates, each well containing 100 µl of RPMI 1640 mediumsupplemented with 1% L-glutamine (200 mM) and 10% fetal bovine serum, and 4000 L-6 cells (a primary cell line derived from rat skeletal myoblasts).[409, 410] Serial drug dilutions of eleven 3-fold dilution steps covering a range from 100 to 0.002 µg/ml were prepared. After 70 hours of incubation the plates were inspected under an inverted microscope to assure growth of the controls and sterile conditions. 10 µl of Alamar Blue was then added to each well and the plates incubated for another 2 hours. Then the plates were read with a Spectramax Gemini XS microplate fluorometer (Molecular Devices Cooperation, Sunnyvale, CA, USA) using an excitation wavelength of 536 nm and an emission wavelength of 588 nm. The IC_{50} values were calculated by linear regression[4] from the sigmoidal dose inhibition curves using SoftmaxPro software (Molecular Devices Cooperation, Sunnyvale, CA, USA). Podophyllotoxine (Sigma P4405) was used as control.

[409] B. Page, M. Page, and C. Noel, *Int. J. Oncol.* **1993**, *3*, 473.

[410] S. A. Ahmed, R. M. Gogal, J. E. Walsh, *J. Immunol. Methods* **1994**, *170*, 211.

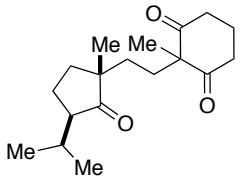
7.5 Synthetic Studies Towards Striatal A

2-(2-((1*R*,3*R*)-3-isopropyl-1-methyl-2-methylenecyclopentyl)ethyl)-2-methylcyclohexane-1,3-dione (5.110):



The diketone **4.55** (7.85 g, 28.4 mmol, 1.0 eq) was dissolved in THF (90 ml) and dried LiCl (5.76 g, 42.6 mmol, 1.5 eq) and DBU (6.55 g, 6.42 ml, 42.6 mmol, 1.5 eq) were added. After stirring at r.t. for 30 minutes. Iodomethane (12.2 g, 5.36 ml, 85.2 mmol, 3.0 eq) was added and the mixture stirred at 80 °C for 15 h. The brown solution was allowed to cool to r.t. and then poured on ice-water (60 ml). The mixture was extracted with Et_2O (4 x 50 ml) and the combined organic layer were dried over Na_2SO_4, filtered and evaporated to obtain a dark-red oil. The crude was purified by flash column chromatograpy (SiO_2, pentane/EtOAc 10:1 to 8:1) to yield the methyldiketone **5.110** (2.77 g, 9.54 mmol, 34%) as a yellow oil. $\mathbf{R_f}$ = 0.76 (SiO_2, pentane/EtOAc 4:1); **Optical rotation**: $[\alpha]_D^{26}$ = +38.7 (*c* 0.08, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 2955, 2870, 1726, 1695, 1459, 1373, 1315, 1270, 1025, 881 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.76 (d, *J* = 2.5 Hz, 1H), 4.72 (d, *J* = 2.9 Hz, 1H), 2.73 – 2.65 (m, 2H), 2.60 – 2.54 (m, 2H), 2.37 – 2.29 (m, 1H), 2.07 – 1.99 (m, 1H), 1.97 – 1.90 (m, 1H), 1.86 – 1.77 (m, 1H), 1.77 – 1.69 (m, 2H), 1.62 – 1.53 (m, 1H), 1.45 – 1.32 (m, 3H), 1.32 – 1.28 (m, 1H), 1.19 (s, 3H), 1.17 – 1.11 (m, 1H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.92 (s, 3H), 0.75 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 210.6, 210.5, 161.9, 103.8, 65.9, 51.3, 45.6, 38.1, 38.0, 36.6, 35.7, 33.4, 28.8, 27.6, 23.1, 22.0, 18.2, 17.9, 16.5; **HRMS (ESI)** m/z calcd for $C_{19}H_{31}O_2$ $[M+H]^+$: 291.2319, found: 291.2318.

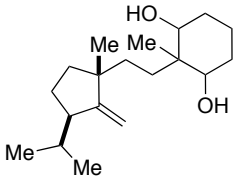
2-(2-((1*R*,3*R*)-3-isopropyl-1-methyl-2-oxocyclopentyl)ethyl)-2-methylcyclohexane-1,3-dione (5.111):



The olefin **5.110** (13.2 mg, 45.4 μmol, 1.0 eq) was dissolved in dry MeOH (2.0 ml) and cooled to −78 °C. O_3 was bubbled through the colorless solution until a persistent blue color was obtained (2 minutes). O_2 was bubbled through the blue solution until a clear colorless solution as obtained.

To the colorless solution DMS (5.7 mg, 6.7 μmol, 2.0 eq) was added and the mixture stirred at −78 °C for 30 min. The colorless solution was allowed to warm to r.t. over 2 h and then evaporated to obtain a colorless oil. The crude material was purified by flash column chromatography (SiO_2, pentane/EtOAc 6:1) to obtain the desired ketone **5.111** (5.3 mg, 18.0 μmol, 40%) as a colorless oil. **R_f** = 0.29 (pentane/EtOAc 4:1); **FTIR (neat):** $\tilde{\nu}$ = 2959, 2872, 1725, 1694, 1459, 1373, 1316, 1132, 1068, 1025, 840 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 2.71 – 2.57 (m, 4H), 2.18 – 2.10 (m, 1H), 2.05 – 1.96 (m, 2H), 1.93 – 1.81 (m, 3H), 1.69 – 1.63 (m, 3H), 1.27 – 1.15 (m, 6H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 3H), 0.79 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 223.4, 210.4, 210.3, 65.5, 55.9, 48.5, 38.1, 33.4, 32.3, 21.0, 27.4, 21.2, 21.0, 20.5, 19.4, 18.5, 17.8; **HRMS (ESI)** m/z calcd for $C_{18}H_{29}O_3$ $[M+H]^+$: 293.2111, found: 293.2110

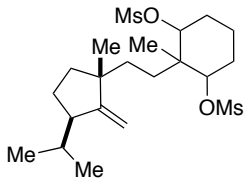
2-(2-((1*R*,3*R*)-3-isopropyl-1-methyl-2-methylenecyclopentyl)ethyl)-2-methylcyclohexane-1,3-diol (5.116):



The diketone **5.110** (6.7 mg, 23.1 μmol, 1.0 eq) was dissolved in THF (0.2 ml) and cooled to 0 °C. LTBA (1.0 M in THF, 47.2 mg, 52.4 μl, 2.5 eq) was slowly added and stirred at 0 °C for 40 minutes and then allowed to stirr at r.t. for 2 h. The mixture was recooled to 0 °C and another portion of LTBA (1.0 M in THF, 47.2 mg, 52.4 ml, 2.5 eq) was added. The mixture was stirred for 1 h at r.t. Sat. aq. NH_4Cl (0.1 ml), aq. HCl (10%, 10 drops) were added and the mixture extracted with EtOAc (3 x 2.0 ml). The combined organic layer were dried over Na_2SO_4, filtered and evaporated. The crude material was purified by flash column chromatography (SiO_2, pentane/EtOAc 7:1) to obtain the diol **5.116** (4.4 mg, 15.0 μmol, 64%) as a colorless oil. **R_f** = 0.63 (SiO_2, pentane/EtOAc 6:1); **Optical rotation:** $[\alpha]_D^{25}$ = +38.5 (*c* 0.15, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3334, 2949, 2870, 1728, 1645, 1455, 1422, 1382, 1253, 1172, 1047, 1102, 948, 878, 631 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.81 (d, *J* = 2.9 Hz, 1H), 4.77 (d, *J* = 2.4 Hz, 1H), 3.62 (bs, 1H), 3.57 (bs, 1H), 2.83 (d, *J* = 8.0 Hz, 1H), 2.66 (d, *J* = 5.9 Hz, 1H), 2.44 – 2.39 (m, 1H), 2.01 – 1.89 (m, 2H), 1.84 – 1.75 (m, 2H), 1.71 – 1.67 (m, 3H), 1.62 – 1.57 (m, 2H), 1.53 –

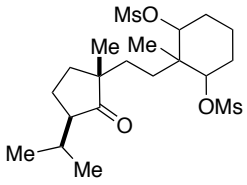
1.46 (m, 2H), 1.43 – 1.36 (m, 4H), 0.99 (s, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.84 (s, 3H), 0.77 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* = 163.9, 102.9, 74.8, 74.3, 51.6, 46.1, 39.6, 36.6, 34.1, 29.7, 28.9, 28.8, 28.8, 27.8, 23.2, 22.1, 20.9, 16.5, 14.2; **HRMS (ESI)** m/z calcd for $C_{19}H_{35}O_2$ $[M+H]^+$: 295.2632, found: 295.2627.

2-(2-((1*R*,3*R*)-3-isopropyl-1-methyl-2-methylenecyclopentyl)ethyl)-2-methylcyclohexane-1,3-diyl dimethanesulfonate (5.117):



The diol **5.116** (128.0 mg, 0.44 mmol, 1.0 eq) was dissolved in py (1.76 ml) and the solution cooled to 0 °C. MsCl (150 mg, 0.1 ml, 1.31 mmol, 3.0 eq) and DMAP (5.32 mg, 43.6 μmol, 0.1 eq) were added. The mixture was stirred at 0 °C for 10 minutes. The mixture was then stirred at r.t. for 15 h. Water (1.0 ml) and aq. HCl (1 M, 1.0 ml) was added and the mixture extracted with Et_2O (3 x 2.0 ml). The combined organic layers were washed with HCl (1 M, 1.0 ml), dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash column chromatography (SiO_2, pentane/EtOAc 5:1 to 3:1) to yield the mesylated product **5.117** (155.0 mg, 0.34 mmol, 79%) as a white solid upon storage at r.t. **M.p.**: 67.8 – 68.9 °C; **R_f** = 0.18 (SiO_2, pentane/EtOAc 4:1); **Optical rotation**: $[\alpha]_D^{25}$ = +17.5 (*c* 0.12, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 2954, 2877, 1465, 1337, 1314, 1170, 961, 906, 865, 805, 760 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* = 4.79 – 4.77 (dd, *J* = 2.9, 4.7 Hz, 2H), 4.50 – 4.45 (m, 2H), 3.02 (s, 3H), 3.02 (s, 3H), 2.41 – 2.35 (m, 1H), 1.97 – 1.89 (m, 6H), 1.63 – 1.57 (m, 2H), 1.50 – 1.38 (m, 7H), 1.11 (s, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.97 (s, 3H), 0.77 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* = 162.6, 103.7, 84.8, 84.5, 51.3, 45.9, 41.5, 39.1, 39.1, 36.9, 34.3, 28.9, 27.5, 27.2, 27.2, 23.2, 22.1, 21.3, 16.6; **HRMS (ESI)** m/z calcd for $C_{21}H_{38}O_6S_2Na$ $[M+Na]^+$: 473.2002, found: 473.2005.

2-(2-((1*R*,3*R*)-3-isopropyl-1-methyl-2-oxocyclopentyl)ethyl)-2-methylcyclohexane-1,3-diyl dimethanesulfonate (5.118):



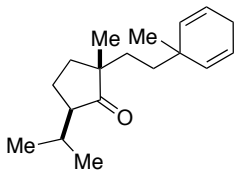
The olefin **5.117** (8.05 mg, 17.9 μmol, 1.0 eq) was dissolved in dry CH_2Cl_2 (2.0 ml) and cooled to −78 °C. O_3 was bubbled through the colorless solution until a persistent blue color was obtained (2 minutes). O_2 was bubbled through the blue solution until a clear colorless solution as obtained. To the colorless solution DMS (2.22 mg, 35.7 μmol, 2.0 eq) was added and the mixture stirred at −78 °C for 30 min. The colorless solution was allowed to warm up to r.t. over 2 h and then evaporated to obtain a colorless oil. The crude material was purified by flash column chromatography (SiO_2, pentane/EtOAc 2:1) to obtain the desired ketone **5.118** (2.42 mg, 5.0 μmol, 30%) as colorless oil and the allylic alcohol **5.119** (2.87 mg, 6.34 mmol, 34%) as colorless oil. $\mathbf{R_f}$ = 0.30 (pentane/EtOAc 2:1); **Optical rotation**: $[\alpha]_D^{25}$ = +31.3 (*c* 0.18, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 2958, 2877, 2327, 1727, 1464, 1332, 1171, 967, 917, 877, 801, 734, 629 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.50 – 4.48 (m, 2H), 3.08 (s, 3H), 3.02 (s, 3H), 2.18 – 2.05 (m, 2H), 1.97 – 1.89 (m, 5H), 1.80 – 1.73 (m, 1H), 1.71 – 1.68 (m, 1H), 1.66 – 1.57 (m, 3H), 1.52 – 1.46 (m, 3H), 1.41 – 1.34 (m, 1H), 1.10 (s, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.93 (s, 3H), 0.80 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 223.9, 84.1, 83.9, 56.2, 48.8, 41.3, 39.2, 39.1, 33.4, 30.7, 27.3, 27.2, 21.7, 21.2, 21.1, 20.6, 18.5.

Alternative procedure

The olefin **5.117** (9.76 mg, 21.7 μmol, 1.0 eq) was dissolved in *t*-BuOH (0.5 ml) and water (0.13 ml). NMO (4.40 mg, 36.8 μmol, 1.7 eq) was added and the mixture cooled to 0 °C. OsO_4 (4% in water, 0.01 ml, 1.1 μmol, 0.05 eq) was added and stirred at r.t. for 2.3 d. Sat. aq. $Na_2S_2O_3$ (0.3 ml) was added and the mixture stirred for 30 minutes. The mixture was extracted with EtOAc (3 x 0.3 ml) and the combined organic layers were dried over Na_2SO_4, filtered and evaporated. The crude material was dissolved in THF (0.16 ml) and water (0.08 ml) and $NaIO_4$ (15.0 mg, 65.2 μmol, 3.2 eq) were added and the mixture stirred for 2.5 h at r.t. EtOAc (0.4 ml) was added, the mixture filtered over

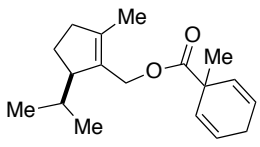
Na_2SO_4 and thoroughly washed with EtOAc (2 x 0.3 ml). The combined organic layers were evaporated and the crude material was purified by flash column chromatography (SiO_2, pentane/EtOAc 2:1) to yield the desired ketone **5.118** (4.79 mg, 11.0 μmol, 51%) as a colorless oil.

(2*R*,5*R*)-5-isopropyl-2-methyl-2-(2-(1-methylcyclohexa-2,5-dien-1-yl)-ethyl)cyclopentan-1-one (5.120):



Mesylate **5.118** (9.3 mg, 20.5 μmol, 1.0 eq) was dissolved in DMF (0.1 ml). Anhydrous LiBr (4.55 mg, 51.4 μmol, 2.5 eq) and Li_2CO_3 (3.87 mg, 51.4 μmol, 2.5 eq) were added and the mixture heated to 140 °C for 4 h. After cooling to r.t. water (0.2 ml) was added and the mixture extracted with Et_2O (3 x 1.0 ml). The combined organic layer was dried over Na_2SO_4, filtered and evaporated. The crude material was purified by flash column chromatography (SiO_2, pentane/EtOAc 98:2) to yield the olefin **5.120** (3.95 mg, 15.0 μmol, 74%) as slightly colorless oil containing small impurities. $\mathbf{R_f}$ = 0.50 (SiO_2, pentane/EtOAc 19:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.71 – 5.66 (m, 2H), 5.38 – 5.32 (m, 2H), 2.57 – 2.55 (m, 2H), 2.18 – 2.11 (m, 1H), 2.09 – 2.03 (m, 1H), 1.93 – 1.86 (m, 1H), 1.70 – 1.58 (m, 4H), 1.36 – 1.30 (m, 3H), 1.01 (s, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 3H), 0.79 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 224.2, 133.9, 133.8, 123.5, 56.0, 48.8, 37.2, 36.1, 33.5, 33.3, 30.2, 27.3, 26.5, 21.5, 21.3, 20.6, 18.5.

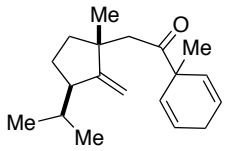
(*R*)-(5-isopropyl-2-methylcyclopent-1-en-1-yl)methyl 1-methylcyclohexa-2,5-diene-1-carboxylate (5.122):



The acid **5.121** (300 mg, 2.17 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (10.0 ml) and DMAP (79.6 mg, 0.65 mmol, 0.3 eq) was added. A solution of the allyl alcohol **4.52** (335 mg, 2.17 mmol, 1.0 eq) in CH_2Cl_2 (6.5 ml) was added at 0 °C. EDC x HCl (832 mg, 4.34 mmol, 2.0 eq) was added and the mixture stirred at 0 °C for 10 minutes. The mixture was allowed to warm to r.t. and stirred for 15 h. The mixture was washed with aq. HCl (5%, 5.0 ml), sat. aq. $NaHCO_3$ (5.0 ml) and water (2 x 3.0 ml). The org. layer was dried over

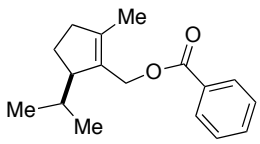
Na_2SO_4, filtered and evaporated. The crude product was purified by flash column chromatography (SiO_2, pentane/Et_2O 20:1) to yield the ester **5.122** (488 mg, 1.78 mmol, 82%) as a colorless oil. $\mathbf{R_f}$ = 0.75 (SiO_2, pentane/Et_2O 19:1); **Optical rotation**: $[\alpha]_D^{25}$ = −17.9 (*c* 0.35, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3033, 2955, 2871, 1727, 1453, 1367, 1268, 1229, 1200, 1106, 944, 703 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.82 – 5.71 (m, 4H), 4.64 (d, *J* = 12.4 Hz, 1H), 4.57 (d, *J* = 12.2 Hz, 1H), 2.73 (bs, 1H), 2.65 – 2.63 (m, 2H), 2.29 – 2.20 (m, 2H), 1.96 – 1.88 (m, 1H), 1.81 – 1.73 (m, 1H), 1.71 (bs, 3H), 1.63 – 1.55 (m, 1H), 1.32 (s, 3H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.67 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 175.4, 139.9, 131.8, 129.0, 124.5, 60.6, 52.8, 44.2, 38.1, 28.9, 27.5, 26.1, 21.9, 21.5, 16.1, 14.3; **HRMS (ESI)** m/z calcd for $C_{18}H_{26}O_2Na$ $[M+Na]^+$: 297.1825, found: 297.1828.

2-((1*R*,3*R*)-3-isopropyl-1-methyl-2-methylenecyclopentyl)-1-(1-methylcyclohexa-2,5-dien-1-yl)ethan-1-one (5.124):



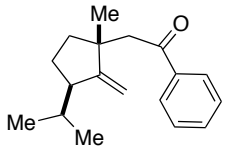
The ester **5.122** (19.6 mg, 71.5 μmol, 1.0 eq) was dissolved in degassed THF (0.6 ml) and Cp_2TiCl_2 (1.78 mg, 7.15 μmol, 0.1 eq) in THF (0.3 ml) was added. Cp_2TiMe_2[366] (17% in toluene, 0.392 ml, 0.36 mmol, 5.0 eq) was added and the Schlenk tube covered with aluminum foil. The mixture was stirred at 65 °C for 22 h. The mixture was allowed to cool to r.t., then diluted with Et_2O (1.5 ml), dried over Na_2SO_4 and filtered over Celite. The crude material was purified by flash column chromatography (basic alumina, pentane/Et_2O/Et_3N 19:1:0.1, spot on top) to yield the enol **5.123** (5.76 mg, 21.0 μmol, 30%) as a yellow oil. The enol **5.123** was directly diluted with toluene (0.5 ml) and stirred for 19 h at 173 °C. The mixture was allowed to cool to r.t. and directly evaporated. The crude material was purified by flash column chromatography (SiO_2, pentane/Et_2O 98:2) to yield the desired ketone **5.124** (3.53 mg, 13.0 μmol, 44%, d.r. = 9:1) as a yellow oil**.** $\mathbf{R_f}$ = 0.73 (SiO_2, pentane/Et_2O 19:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.88 – 5.84 (m, 2H), 5.53 – 5.47 (m, 2H), 4.70 (dd, *J* = 8.3, 3.1 Hz, 2H), 2.77 – 2.59 (m, 3H), 2.59 – 2.53 (m, 1H), 2.00 – 1.94 (m, 1H), 1.64 – 1.58 (m, 4H), 1.17 (s, 3H), 0.99 (s, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.76 (d, *J* = 6.7 Hz, 3H).

(*R*)-(5-isopropyl-2-methylcyclopent-1-en-1-yl)methyl benzoate (5.126):



The acid **5.125** (200 mg, 1.64 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (7.6 ml) and DMAP (60.6 mg, 0.49 mmol, 0.3 eq) was added. A solution of the allyl alcohol **4.52** (253 mg, 1.64 mmol, 1.0 eq) in CH_2Cl_2 (4.9 ml) was added at 0 °C. EDC x HCl (634 mg, 3.28 mmol, 2.0 eq) was added and stirred at 0 °C for 10 minutes. The mixture was allowed to warm to r.t. and stirred for 22 h. The mixture was washed with aq. HCl (5%, 4.0 ml), sat. aq. $NaHCO_3$ (4.0 ml) and water (2 x 2.5 ml). The org. layer was dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash column chromatography (SiO_2, pentane/Et_2O 20:1) to yield the ester **5.126** (370 mg, 1.43 mmol, 88%) as a colorless oil. $\mathbf{R_f}$ = 0.73 (SiO_2, pentane/Et_2O 19:1); **Optical rotation**: $[\alpha]_D^{24}$ = –17.7 (*c* 0.24, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 2956, 2871, 2843, 1717, 1603, 1452, 1381, 1314, 1268, 1175, 1110, 1069, 1026, 936, 713, 632 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.05 – 8.02 (m, 2H), 7.55 (tt, *J* = 7.5, 1.3 Hz, 1H), 7.46 – 7.41 (m, 2H), 4.91 (d, *J* = 12.1 Hz, 1H), 4.80 (d, *J* = 12.2 Hz, 1H), 2.85 (bs, 1H), 2.32 – 2.27 (m, 2H), 2.07 – 2.00 (m, 1H), 1.86 – 1.76 (m, 4H), 1.67 – 1.58 (m, 1H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.73 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 166.9, 140.7, 132.9, 131.8, 130.7, 129.7, 128.5, 60.4, 53.0, 38.1, 29.0, 22.0, 21.6, 16.1, 14.3; **HRMS** (ESI) m/z calcd for $C_{17}H_{22}O_2Na$ $[M+Na]^+$: 281.1512, found: 281.1515.

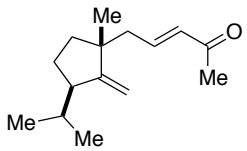
2-((1*R*,3*R*)-3-isopropyl-1-methyl-2-methylenecyclopentyl)-1-phenylethan-1-one (5.128):



The ester **5.126** (24.5 mg, 94.8 μmol, 1.0 eq) was dissolved in degassed THF (0.8 ml) and Cp_2TiCl_2 (2.36 mg, 9.48 μmol, 0.1 eq) in THF (0.3 ml) was added. Cp_2TiMe_2[366] (17% in toluene, 0.61 ml, 0.47 mmol, 5.0 eq) was added and the Schlenk tube covered with aluminium foil. The mixture was stirred at 65 °C for 13 h. The mixture was allowed to cool to r.t. and then diluted with Et_2O (2.0 ml) and dried over Na_2SO_4 and filtered over Celite. The crude material was purified by flash column chromatography (basic alumina, pentane/Et_2O/Et_3N 100:1:0.5, spot on top) to yield the enol **5.127** as a colorless oil. The enol

5.127 was directly diluted with toluene (1.0 ml) and stirred for 19 h at 100 °C. The mixture was allowed to cool to r.t. and directly evaporated. The crude was purified by flash column chromatography (SiO_2, pentane/Et_2O 95:5) to yield the desired ketone **5.128** (18.9 mg, 73.0 μmol, 79% over two steps) as a colorless oil. **R_f** = 0.61 (SiO_2, pentane/Et_2O 19:1); **Optical rotation**: $[\alpha]_D^{25}$ = +41.1 (*c* 0.17, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3327, 3065, 2957, 2870, 1690, 1674, 1597, 1448, 1351, 1238, 1198, 1106, 1003, 882, 751, 691, 657, 625 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.95 – 7.92 (m, 2H), 7.45 (td, *J* = 7.3, 2.1 Hz, 1H), 7.47 – 7.42 (m, 2H), 4.86 (d, *J* = 3.0 Hz, 1H), 4.79 (d, *J* = 2.7 Hz, 1H), 3.20 (d, *J* = 16.3 Hz, 1H), 3.08 (d, *J* = 16.3 Hz, 1H), 2.63 – 2.56 (m, 1H), 2.05 – 1.94 (m, 1H), 1.82 – 1.75 (m, 1H), 1.70 – 1.62 (m, 2H), 1.48 – 1.38 (m, 1H), 1.12 (s, 3H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 199.7, 163.1, 138.5, 132.8, 128.6, 128.6, 128.2, 103.6, 50.8, 49.1, 45.0, 37.4, 28.8, 27.6, 23.4, 22.0, 16.6; **HRMS (ESI)** m/z calcd for $C_{18}H_{24}O_1Na$ $[M+Na]^+$: 279.1719, found: 279.1719.

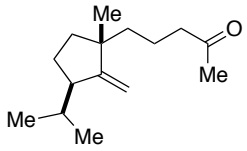
(*E*)-5-((1*R*,3*R*)-3-isopropyl-1-methyl-2-methylenecyclopentyl)pent-3-en-2-one (5.144):



LiCl (112 mg, 2.63 mmol, 2.5 eq) was dried and suspended in ACN (6.0 ml). Dimethyl 2-oxopropylphosphonate (437 mg, 2.63 mmol, 2.5 eq) and DIPEA (313 mg, 0.4 ml, 2.42 mmol, 2.3 eq) were added. The mixture was stirred at r.t. for 20 minutes and a solution of the aldehyde **4.54** (190 mg, 1.05 mmol, 1.0 eq) in ACN (2.0 ml) was added at r.t. and the mixture stirred for 5 h at r.t. Brine (2.0 ml) was added and the mixture extracted with EtOAc (3 x 4.5 ml). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The crude oil was purified by flash column chromatography (SiO_2, pentane/Et_2O 19:1) to yield the desired unsaturated ketone **5.144** (183 mg, 0.83 mmol, 79%) as a colorless oil. **R_f** = 0.19 (SiO_2, pentane/Et_2O 19:1); **Optical rotation**: $[\alpha]_D^{25}$ = +79.6 (*c* 0.51, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3215, 3113, 2945, 2867, 1700, 1643, 1595, 1507, 1464, 1417, 1361 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.79 – 6.71 (m, 1H), 6.07 (dt, *J* = 15.9, 1.4 Hz, 1H), 4.85 – 4.84 (m, 2H), 2.44 – 2.36 (m, 1H), 2.33 – 2.31 (m, 2H), 2.24 (s, 3H), 2.00 – 1.93 (m, 1H), 1.66 – 1.58 (m, 1H), 1.53 – 1.49 (m, 1H), 1.47 – 1.39 (m, 2H),

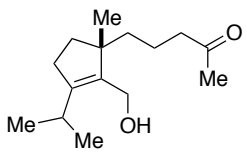
1.02 (s, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* = 198.7, 161.6, 146.2, 133.5, 104.5, 51.1, 46.1, 44.9, 37.2, 29.1, 27.6, 27.1, 23.2, 22.0, 16.7; **HRMS (ESI)** m/z calcd for $C_{15}H_{25}O$ $[M+H]^+$: 221.1900, found: 221.1897.

5-((1*S*,3*R*)-3-isopropyl-1-methyl-2-methylenecyclopentyl)pentan-2-one (5.145):



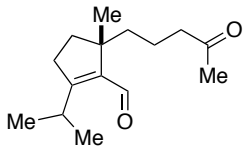
Toluene (2.7ml) and *t*-BuOH (0.13 ml) were degassed and added to a mixture of $Cu(OAc)_2$ (14.6 mg, 71.9 μmol, 0.1 eq) and 1.2-bis(diphenylphospino)benzene (16.4 mg, 35.9 μmol, 0.05 eq). The mixture was stirred for 20 minutes at r.t. and PMHS (0.1 ml) was added and the blue solution turned green to yellow over 10 minutes. A solution of the unsaturated ketone **5.144** (158 mg, 0.72 mmol, 1.0 eq) in a mixture of toluene (3.0 ml) and *t*-BuOH (0.14 ml) was added to the green/yellow solution. The mixture was stirrred at r.t. for 2.5 h and then diluted with EtOAc (8.0 ml) and washed with aq. NaOH (1 M, 3.0 ml), aq. HCl (1 M, 3.0 ml) and brine (3.0 ml). The combined aq. layers were rextracted with EtOAc (4.0 ml) and the combined organic layers were dried over Na_2SO_4, filtered and evaporated. The crude was purified by flash column chromatography (SiO_2, pentane/Et_2O 19:1) to obtain ketone **5.145** (127 mg, 0.57 mmol, 80%) as a colorless oil. **R_f** = 0.28 (SiO_2, pentane/Et_2O 19:1); **Optical rotation**: $[\alpha]_D^{25}$ = +45.4 (*c* 0.21, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3068, 2954, 2870, 1717, 1645, 1510, 1462, 1517, 1366, 1269, 1165, 1053, 1029, 880, 779, 675, 628 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* = 4.76 (dd, *J* = 5.3, 2.7 Hz, 2H), 2.39 (t, *J* = 7.2 Hz, 3H), 2.12 (s, 3H), 2.01 – 1.90 (m, 1H), 1.62 – 1.55 (m, 2H), 1.54 – 1.47 (m, 2H), 1.44 – 1.37 (m, 3H), 1.33 – 1.26 (m, 1H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.95 (s, 3H) 0.77 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* = 209.5, 140.4, 134.9, 50.3, 44.7, 39.3, 34.9, 30.0, 28.3, 27.2, 25.7, 21.5, 21.2, 19.5, 9.4; **HRMS (ESI)** m/z calcd for $C_{15}H_{27}O$ $[M+H]^+$: 223.2056, found: 223.2055.

(*S*)-5-(2-(hydroxymethyl)-3-isopropyl-1-methylcyclopent-2-en-1-yl)pentan-2-one (5.147):



The olefin **5.145** (1.18 g, 5.31 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (50.0 ml) and the solution cooled to 0 °C. *m*-CPBA (2.09 g, 8.49 mmol, 1.6 eq) was added and the mixture stirred at 0 °C for 10 minutes and then at r.t. for 4 h. The mixture was diluted with EtOAc (20.0 ml) and washed with sat. $Na_2S_2O_3$ (9.0 ml), sat. aq. $NaHCO_3$ (9.0 ml) and brine (9.0 ml). The organic layer was dried over Na_2SO_4, filtered and evaporated. The crude material was purified by flash column chromatography (SiO_2, pentane/Et_2O 3:1) to yield the allylic alcohol **5.147** (900 mg, 3.77 mmol 71%) as a colorless oil. $\mathbf{R_f}$ = 0.30 (SiO_2, pentane/Et_2O 3:1); **Optical rotation**: $[\alpha]_D^{25}$ = +19.8 (*c* 0.33, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 2956, 2873, 1716, 1575, 1462, 1367, 1229, 1166, 995, 927, 817, 753, 675, 628 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.08 (m, 2H), 2.86 (hept, *J* = 6.9 Hz, 1H), 2.48 – 2.37 (m 2H), 2.27 – 2.18 (m, 2H), 2.12 (s, 3H), 1.78 – 1.72 (m, 1H), 1.54 – 1.45 (m, 5H), 1.36 – 1.32 (m, 2H), 1.04 (s, 3H), 1.02 (d, *J* = 7.0 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 209.7, 148.5, 138.7, 56.0, 50.1, 44.1, 40.3, 35.4, 30.2, 28.4, 27.3, 27.0, 22.0, 21.7, 19.0; **HRMS (ESI)** m/z calcd for $C_{15}H_{27}O_2$ $[M+H]^+$: 239.2006, found: 239.2004.

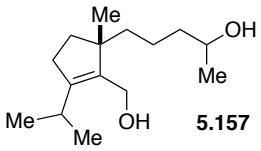
(*S*)-2-isopropyl-5-methyl-5-(4-oxopentyl)cyclopent-1-ene-1-carbaldehyde (5.148):



The allylic alcohol **5.147** (172 mg, 72.3 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (10.0 ml) and DMP (501 mg, 1,16 mmol, 1.6 eq) was added and the mixture stirred at r.t. for 19 h. EtOAc (10.0 ml) was added and the mixture washed with sat. $Na_2S_2O_3$ (5.0 ml), sat. aq. $NaHCO_3$ (5.0 ml) and brine (5.0 ml) and the organic layer was dired over Na_2SO_4, filtered and evaporated. The crude material was purified by flash column chromatography (SiO_2, pentane/Et_2O 3:1) to obtain the aldeyhde **5.148** (119 mg, 0.50 mmol, 70%) as a colorless oil. $\mathbf{R_f}$ = 0.17 (SiO_2, pentane/Et_2O 3:1); **Optical rotation**: $[\alpha]_D^{25}$ = +2.5 (*c* 0.21, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 2957, 2872, 1713, 1668, 1616, 1459, 1409, 1363, 1260, 1230, 1168, 1132, 631 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 10.0 (s,

1H), 3.46 – 3.39 (m, 1H), 2.48 – 2.44 (m, 2H), 2.40 – 2.37 (m, 2H), 2.11 (s, 3H), 1.86 – 1.78 (m, 1H), 1.68 – 1.59 (m, 1H), 1.56 – 1.47 (m, 3H), 1.33 – 1.27 (m, 1H), 1.17 (s, 3H), 1.13 (d, *J* = 6.9 Hz, 3H), 1.11 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* = 209.4, 188.4, 173.0, 141.4, 49.6, 44.4, 38.7, 35.1, 30.2, 30.1, 26.9, 25.9, 21.9, 21.7, 19.5; **HRMS (ESI)** m/z calcd for $C_{15}H_{25}O_2$ $[M+H]^+$: 237.1849, found: 237.1852.

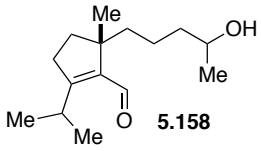
5-((*S*)-2-(hydroxymethyl)-3-isopropyl-1-methylcyclopent-2-en-1-yl)pentan-2-ol (5.157):



5.157

The ketone **5.147** (81.4 mg, 0.34 mmol, 1.0 eq) was dissolved in dry THF (8.0 ml) and cooled to 0 °C. $LiAlH_4$ (15.9 mg, 0.41 mmol, 1.2 eq) was added and stirred at 0 °C. Sat. aq NH_4Cl (1.8 ml) was added slowly after 1 h at 0 °C and then extracted (3 x 3.0 ml) with Et_2O. The combined organic layers were washed with sat. aq NH_4Cl (1.5 ml) and brine (2 x 1.5 ml). The organic layer was dried over Na_2SO_4, filtered and evaporated to obtain a colorless oil. The crude material was purified by flash column chromatography (SiO_2, pentane/Et_2O 1:1) to obtain the secondary alcohol **5.157** (82.1 mg, 0.34 mmol, quant., combined diastereomers) as a colorless oil. $\mathbf{R_f}$ = 0.30 (SiO_2, pentane/Et_2O 1:1); **FTIR (neat):** $\tilde{\nu}$ = 3385, 2957, 2873, 1462, 1376, 1126, 986, 928, 820, 677, 630 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* = 4.15 – 4.02 (m, 4H), 3.86 – 3.75 (m, 2H), 2.83 (hept, *J* = 7.0 Hz, 2H), 2.28 – 2.16 (m, 4H), 1.79 – 1.69 (m, 2H), 1.56 – 1.54 (m, 3H), 1.52 – 1.48 (m, 2H), 1.47 – 1.36 (m, 7H), 1.35 – 1.20 (m, 6H), 1.17 – 1.15 (m, 6H), 1.94 (s, 3H), 1.04, (s, 3H), 1.02 – 0.98 (m, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* = 148.5, 148.2, 139.3, 138.6, 68.3, 67.1, 56.1, 56.1, 50.1, 50.0, 40.7, 40.1, 40.0, 39.5, 35.7, 35.3, 28.5, 28.3, 27.4, 27.3, 27.2, 26.5, 23.7, 23.7, 22.0, 22.0, 21.7, 21.7, 21.2, 20.6; **HRMS (ESI)** m/z calcd for $C_{15}H_{29}O_2$ $[M+H]^+$: 241.2162, found: 241.2158.

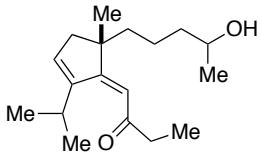
(5*S*)-5-(4-hydroxypentyl)-2-isopropyl-5-methylcyclopent-1-ene-1-carbaldehyde (5.158):



5.158

Allylic alcohol **5.157** (41.5 mg, 0.173 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (1.0 ml) and $BaMnO_4$ (197 mg, 0.69 mmol, 4.0 eq) and added and stirred for 19 h at r.t. The mixture was diluted with CH_2Cl_2 (1.0 ml) and filtered over Celite and washed with CH_2Cl_2 (2 x 1.0 ml). The combined organic layers were evaporated and the residue purified by flash column chromatography (SiO_2, pentane/Et_2O 1:1) to obtain aldehyde **5.158** (36.4 mg, 0.11 mmol, 64%) as colorless oil, which was directly used in the next step. $\mathbf{R_f}$ = 0.28 (SiO_2, pentane/Et_2O 1:1).

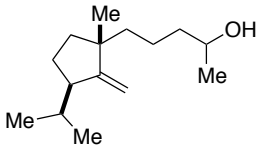
(*Z*)-1-((5*S*)-5-(4-hydroxypentyl)-2-isopropyl-5-methylcyclopent-2-en-1-ylidene)butan-2-one (5.161):



Diisopropylamine (84.6 mg, 0.12 ml, 0.84 mmol, 11.0 eq) was dissolved in THF (1.0 ml) and the solution cooled to −78 °C. *n*-BuLi (0.52 ml, 1 M in THF, 0.84 mmol, 11.0 eq) was added and the mixture stirred at −78 °C for 35 minutes. 1.2-Dibromopropane was added and the mixture stirred at r.t. for 20 minutes. The mixture was cooled to −78 °C and a solution of the aldehyde **5.158** (18.1 mg, 76.0 μmol, 1.0 eq) in THF (0.8 ml) was added and the mixture stirred at r.t. for 17 h. Water (0.3 ml) and Et_2O (2.0 ml) were added and the organic layer was washed with brine (0.4 ml), dried over Na_2SO_4, filtered and evaporated. The crude material was purified by flash column chromatography (SiO_2, pentane/Et_2O 1:1) to obtain the alkyne **5.159** (18.0 mg, 65.0 μmol, 85%) as slightly yellow oil. The alkyne **5.159** (5.0 mg, 18.0 μmol, 1.0 eq) was dissolved in CH_2Cl_2 (0.32 ml) and EtOH (0.08 ml) and $Cu(OTf)_2$ (0.33 mg, 0.9 μmol, 0.05 eq) were added and the mixture stirred at r.t. for 2.5 h. The crude mixture was directly evaporated and the residue was purified by flash column chromatography (SiO_2, pentane/Et_2O 1:1) to obtain the ketone **5.161** (3.2 mg, 11.0 μmol, 64%) as a brown oil. $\mathbf{R_f}$ = 0.40 (SiO_2, pentane/Et_2O 1:1); **Optical rotation**: $[\alpha]_D^{26}$ = +25.1 (*c* 0.10, $CHCl_3$); **FTIR (neat):** $\tilde{\nu}$ = 3414, 2962, 2927, 2870, 1679, 1575, 1459, 1376, 1299, 1124, 1044, 1010, 856, 803, 667, 626 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.23 (t, *J* = 2.9 Hz, 1H), 6.08 (d, *J* = 4.3

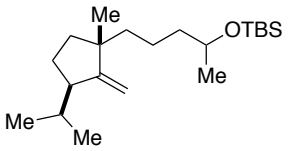
Hz, 1H), 3.83 – 3.72 (m, 1H), 2.54 – 2.48 (m, 3H), 2.25 – 2.20 (m, 1H), 1.66 – 1.57 (m, 1H), 1.51 – 144 (m, 1H), 1.44 – 1.34 (m, 3H), 1.30 (d, *J* = 10.4 Hz, 3H), 1.15 – 1.07 (m, 15H); **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* = 201.5, 201.0, 170.1, 169.8, 151.5, 151.4, 139.1, 139.0, 115.7, 115.5, 68.2, 67.6, 47.7, 47.3, 47.3, 39.9, 39.7, 38.2, 38.2, 38.2, 38.0, 26.1, 25.7, 25.7, 25.6, 23.6, 23.6, 22.3, 22.3, 22.1, 22.1, 21.4, 21.2, 8.8; **HRMS (ESI)** m/z calcd for $C_{18}H_{31}O_2$ $[M+H]^+$: 279.2319, found: 279.2315.

5-((1*S*,3*R*)-3-isopropyl-1-methyl-2-methylenecyclopentyl)pentan-2-ol (5.165):



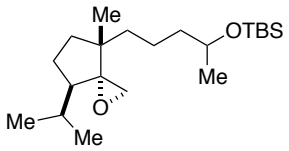
The ketone **5.145** (233 mg, 1.05 mmol, 1.0 eq) was dissolved in THF (10.0 ml) and the solution cooled to 0 °C. $LiAlH_4$ (48.7 mg, 1.26 mmol, 1.2 eq) was added and the mixture stirred for 70 minutes at 0 °C. EtOAc (5.0 ml), sat. aq. NH_4Cl (3.0 ml) was added at 0 °C. The mixture was allowed to warm to r.t. The organic layer was washed with sat. aq. NH_4Cl (3.0 ml) and brine (3.0 ml). The combined aq. layers were extracted with EtOAc (3.0 ml) and the combined organic layers were dried over Na_2SO_4, filtered and evaporated. The crude material was purified by flash column chromatography (SiO_2, pentane/Et_2O 3:1) to obtain the secondary alcohol **5.165** (186 mg, 0.83 mmol, 79% combined diastereomers) as a colorless oil. (Only the major diastereomer could be obtained in pure form and is described here). **R_f** = 0.27 (SiO_2, pentane/Et_2O 3:1); **FTIR (neat):** $\tilde{\nu}$ = 2955, 2871, 1461, 1369, 1129, 879, 632, 534 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* = 4.76 (dd, *J* = 9.4, 2.7 Hz, 1H), 3.80 (dt, *J* = 11.6, 5.9 Hz, 1H), 2.44 – 2.36 (m, 2H), 2.02 – 1.90 (m, 2H), 1.63 – 1.56 (m, 3H), 1.51 – 1.47 (m, 2H), 1.46 – 1.37 (m, 11H), 1.35 – 1.31 (m, 3H), 1.30 – 1.28 (m, 3H), 1.18 (d, *J* = 6.2 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.95 (s, 3H), 0.77 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* = 163.1, 163.0, 103.2, 103.2, 68.3, 68.3, 51.4, 51.3, 46.0, 42.0, 42.0, 40.3, 40.3, 37.1, 37.0, 28.9, 28.9, 27.5, 27.4, 23.7, 23.7, 23.2, 22.1, 21.1, 21.1, 16.6; **HRMS (ESI)** m/z calcd for $C_{15}H_{28}ONa$ $[M+Na]^+$: 247.2032, found: 247.2034.

***tert*-butyl((5-((1*S*,3*R*)-3-isopropyl-1-methyl-2-methylenecyclopentyl)pentan-2-yl)oxy)dimethylsilane (5.166):**



The alcohol **5.165** was used as a diastereomeric mixture. The alcohol **5.165 (**178 mg, 0.79 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (18.0 ml) and 2.6-lutidine (339 mg, 0.37 ml, 3.16 mmol, 4.0 eq) was added and the mixture was cooled to −20 °C. TBSOTf (418 mg, 0.36 ml, 1.58 mmol, 2.0 eq) was added and the mixture stirred at −20 °C for 10 minutes and then at r.t. for another 14 h. Water (5.0 ml) was added and the mixture extracted with CH_2Cl_2 (3 x 5.0 ml). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The crude material was purified by flash column chromatography (SiO_2, pentane) to obtain the protected alcohol **5.166** (253 mg, 0.75 mmol, 95%) as a colorless oil. $\mathbf{R_f}$ = 0.32 (SiO_2, pentane); **FTIR (neat):** $\tilde{\nu}$ = 2957, 2866, 2374, 1462, 1371, 1255, 1133, 880, 835, 773, 632, 537 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.75 (dd, J = 6.7, 2.7 Hz, 4H), 3.82 – 3.71 (m, 2H), 2.43 – 2.33 (m, 2H), 2.05 – 1.87 (m, 2H), 1.64 – 1.27 (m, 20H), 1.11 (d, J = 6.2 Hz, 6H), 0.97 (d, J = 6.9 Hz, 6H), 0.95 (s, 6H), 0.88 (s, 18H), 0.77 (d, J = 6.8 Hz, 6H), -0.04 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 163.2, 163.1, 103.1, 69.0, 68.9, 51.4, 51.3, 46.1, 42.3, 42.2, 40.8, 40.7, 37.2, 37.1, 29.0, 28.9, 27.4, 27.3, 26.1, 24.1, 24.1, 23.3, 22.1, 21.3, 18.3, 16.7, 0.2, -4.2, -4.2, -4.5, -4.5; **HRMS (ESI)** m/z calcd for $C_{21}H_{43}OSi$ $[M+H]^+$: 339.3078, found: 339.3076.

***tert*-butyl((5-((3*R*,4*S*,7*R*)-7-isopropyl-4-methyl-1-oxaspiro[2.4]heptan-4-yl)pentan-2-yl)oxy)dimethylsilane (5.167):**



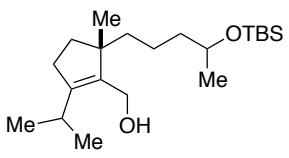
The olefin **5.166** was used as a diastereomeric mixture. Olefin **5.166** (50.0 mg, 0.15 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (1.5 ml) and the solution cooled to 0 °C. $NaHCO_3$ (37.2 mg, 0.44 mmol, 3.0 eq) and *m*-CPBA (51.0 mg, 0.21 mmol, 1.4 eq) was added. The mixture was stirred at 0 °C for 10 minutes and then allowed to warm to r.t. After 19 h, the mixture was quenched with EtOAc (3.0 ml) and then washed with sat. aq. $Na_2S_2O_3$ (1.0 ml), sat. aq. $NaHCO_3$ (2 x 1.0 ml) and brine (1.0 ml). The combined aq. layers were extracted with

EtOAc (2 x 1.0 ml) and the combined organic layers were dried over Na_2SO_4, filtered and evaporated. The crude material was purified by flash column chromatography (SiO_2, pentane/Et_2O 30:1) to obtain the epoxide **5.167** (41.7 mg, 0.12 mmol, 80%, combined diastereomers) as colorless oil.

1st diastereomer **5.167a** (7.05 mg, 19.5 μmol, 13%: $\mathbf{R_f}$ = 0.41 (SiO_2, pentane/Et_2O 30:1); **FTIR (neat):** $\tilde{\nu}$ = 2954, 2930, 2857, 1462, 1373, 1254, 1133, 1063, 834, 773 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.81 – 3.73 (m, 2H), 2.69 (dd, *J* = 4.8, 2.1 Hz, 2H), 2.56 (d, *J* = 4.8 Hz, 2H) 2.08 – 2.02 (m, 2H), 1.66 – 1.57 (m, 4H), 1.54 – 1.42 (m, 6H), 1.41 – 1.28 m, 6H), 1.25 – 1.14 (m, 6H), 1.11 (d, *J* = 6.0 Hz, 6H), 0.90 – 0.88 (m, 24H), 0.86 (d, *J* = 2.8 Hz, 6H), 0.80 (m, 6H), 0.04 (m, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 69.9, 69.9, 68.8, 68.8, 48.8, 48.8, 47.2, 47.1, 42.7, 40.8, 40.8, 39.7, 39.6, 36.3, 36.2, 26.5, 26.1, 26.1, 24.1, 24.0, 23.3, 23.3, 22.8, 21.1, 21.0, 20.7, 20.5, 19.4, 18.3, -4.1, -4.2, -4.5, -4.5; **HRMS (ESI)** m/z calcd for $C_{21}H_{43}O_2Si$ $[M+H]^+$: 355.3027, found: 355.3027.

2nd diastereomer **5.167b** (34.7 mg, 99.0 μmol, 66%: $\mathbf{R_f}$ = 0.30 (SiO_2, pentane/Et_2O 30:1); **FTIR (neat):** $\tilde{\nu}$ = 3326, 2956, 2930, 2858, 1463, 1375, 1252, 1138, 1064, 1042, 988, 834, 806, 772, 665 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.81 – 3.74 (m, 2H), 2.78 (d, *J* = 4.4 Hz, 2H), 2.60 (d, *J* = 4.5 Hz, 2H), 2.06 (ddd, *J* = 11.7, 7.8, 4.2 Hz, 2H), 1.71 – 1.64 (m, 2H), 1.60 – 1.54 (m, 6H), 1.46 – 1.16 (m, 14H), 1.11 (d, *J* = 6.0 Hz, 6H), 1.04 – 0.97 (m, 2H), 0.90 – 0.86 (m, 28H), 0.84 (d, *J* = 6.9 Hz, 6H), 0.04 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 71.2, 71.2, 68.9, 68.8, 49.8, 49.8, 49.1, 49.1, 42.0, 42.0, 40.8, 40.8, 37.2, 37.1, 37.1, 37.0, 26.6, 26.1, 26.1, 24.1, 23.2, 23.1, 22.1, 22.1, 22.1, 21.0, 20.9, 18.3, 17.9, 17.9, -4.2, -4.5, -4.5; **HRMS (ESI)** m/z calcd for $C_{21}H_{43}O_2Si$ $[M+H]^+$: 355.3027, found: 355.3027.

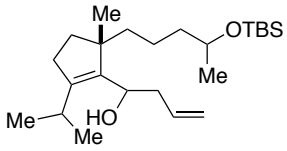
((5*S*)-5-(4-((*tert*-butyldimethylsilyl)oxy)pentyl)-2-isopropyl-5-methylcyclopent-1-en-1-yl)methanol (5.168):



The epoxide **5.167** (53.9 mg, 0.15 mmol, 1.0 eq) was dissolved in EtOAc (1.4 ml) and SiO_2 (400 mg) was added. The mixture was heated to 105 °C for 24 h. After cooling to r.t. the mixture was evaporated. The crude material was purified by

flash column chromatography (SiO_2, pentane/Et_2O 6:1) to obtain the allylic alcohol **5.168** (36.1 mg, 0.10 mmol, 67%, diastereomeric mixture) as colorless oil. $\mathbf{R_f}$ = 0.43 (SiO_2, pentane/Et_2O 5:1); **FTIR (neat):** $\tilde{\nu}$ = 2956, 2929, 2859, 1463, 1373, 1361, 1254, 1134, 1064, 1038, 992, 834, 773, 664, 630, 537 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.13 – 4.01 (m, 2H), 3.80 – 3.72 (m, 1H), 2.84 (hept, *J* = 6.7, 1.4 Hz, 1H), 2.29 – 2.16 (m, 2H), 1.77 – 1.70 (m, 1H), 1.54 – 1.46 (m, 1H), 1.44 – 1.28 (m, 5H), 1.26 – 1.13 (m, 2H), 1.10 (dd, *J* = 6.1, 1.0 Hz, 1H), 1.05 (d, *J* = 2.2 Hz, 1H), 1.03 – 0.98 (m, 2H), 0.88 (d, *J* = 0.9 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 148.2, 148.1, 139.6, 139.4, 69.0, 68.8, 56.2, 56.2, 50.1, 50.0, 41.0, 40.8, 40.8, 40.7, 35.6, 35.6, 28.3, 28.3, 27.3, 27.3, 26.9, 26.7, 26.1, 24.1, 24.0, 21.9, 21.9, 21.9, 21.8, 21.4, 18.3, -4.2, -4.5, -4.5; **HRMS (ESI)** m/z calcd for $C_{21}H_{42}O_2SiNa$ $[M+Na]^+$: 377.2846, found: 377.2847.

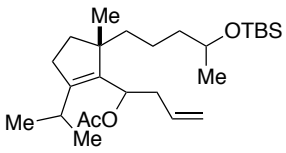
1-((5*S*)-5-(4-((*tert*-butyldimethylsilyl)oxy)pentyl)-2-isopropyl-5-methylcyclopent-1-en-1-yl)but-3-en-1-ol (5.170):



The allylic alcohol **5.168** (463 mg, 1.31 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (30 ml) and pyridinium dichromate (551 mg, 1.44 mmol, 1.1 eq) was added at r.t. After stirring for 3.5 h, EtOAc (8.0 ml) was added and the mixture filtered over Celite and the filter cake washed thoroughly with EtOAc (2 x 5.0 ml). The organic layer was washed with sat. aq. $NaHCO_3$ (5.0 ml) and brine (4.0 ml). The organic layer was dried over Na_2SO_4, filtered and evaporated. The crude mixture was dissolved in THF (18.0 ml) and cooled to −78 °C. Allylmagnesium bromide (3.88 ml, 1 M in Et_2O, 3.88 mmol, 3.0 eq) was added. After stirring at −78 °C for 5 minutes the cooling bath was removed and stirring continued for 1 h. The mixture was cooled to 0 °C, diluted with Et_2O (9.0 ml) and washed with sat. aq. NH_4Cl (5.0 ml) and sat. aq. $NaHCO_3$ (5.0 ml). The combined aq. layers were extracted with Et_2O (5.0 ml) and the combined organic layers were washed with brine (5.0 ml) and then dried over Na_2SO_4, filtered and evaporated. The crude material was purified by flash column chromatography (SiO_2, pentane/Et_2O 15:1) to obtain the allylated alcohol **5.170** (321 mg, 0.81 mmol, 63%, complex diastereomeric mixture) as a colorless oil. $\mathbf{R_f}$ = 0.30

(SiO_2, pentane/Et_2O 15:1); **FTIR (neat):** $\tilde{\nu}$ = 2957, 2930, 2858, 1640, 1463, 1373, 1361, 1254, 1134, 1036, 1004, 912, 834, 773, 664, 627, 544 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.93 – 5.78 (m, 2H), 5.13 – 5.04 (m, 4H), 4.20 (dt, *J* = 10.0, 3.3 Hz, 1H), 4.12 (ddd, *J* = 10.3, 7.2, 3.7 Hz, 1H), 3.78 – 3.68 (m, 2H), 3.19 – 3.02 (m, 2H), 2.51 – 2.42 (m, 2H), 2.28 – 2.19 (m, 2H), 2.16 – 2.12 (m, 3H), 1.77 – 1.60 (m, 3H), 1.52 – 1.19 (m, 15H), 1.10 – 1.02 (m, 11H), 0.98 – 0.92 (m, 13H), 0.86 – 0.81 (m, 19H), 0.00 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 146.1, 146.1, 145.9, 145.9, 141.6, 141.4, 141.4, 141.2, 136.3, 136.3, 117.5, 117.5, 117.4, 69.0, 69.0, 68.8, 68.5, 68.5, 68.5, 50.8, 50.6, 50.5, 42.7, 42.5, 42.5, 41.4, 41.1, 40.8, 40.8, 40.8, 40.7, 40.4, 36.0, 35.9, 35.8, 35.7, 27.9, 27.9, 27.9, 27.9, 27.6, 27.6, 27.1, 26.8, 26.3, 26.1, 26.0, 24.1, 24.1, 24.6, 24.0, 21.8, 21.7, 21.6, 21.5, 21.4, 21.4, 21.4, 21.3, 18.3, 18.3, -4.2, -4.5, -4.5, -4.5; **HRMS (ESI)** m/z calcd for $C_{24}H_{46}O_2SiNa$ $[M+Na]^+$: 417.3159, found: 417.3161.

1-((5*S*)-5-(4-((*tert*-butyldimethylsilyl)oxy)pentyl)-2-isopropyl-5-methylcyclopent-1-en-1-yl)but-3-en-1-yl acetate (5.172):



The secondary alcohol **5.170** (35.9 mg, 91 μmol, 1.0 eq) was dissolved in CH_2Cl_2 (0.3 ml) and cooled to 0 °C. Et_3N (13.8 mg, 19.2 μl, 0.14 mmol, 1.5 eq), Ac_2O (13.9 mg, 12.8 μl, 0.14 mmol, 1.5 eq) and DMAP (1.11 mg, 91.0 μmol, 0.1 eq) were added. The reaction was stirred at 0 °C for 1 h and then at r.t. for 30 minutes. EtOAc (0.5 ml) was added and the mixture washed with sat. aq. $NaHCO_3$ (0.3 ml) and brine (0.3 ml). The combined aq. layer were extracted with EtOAc (0.5 ml) and the combined organic layer was dried over Na_2SO_4, filtered and evaporated. The crude material was purified by flash column chromatography (SiO_2, pentane/Et_2O 30:1) to obtain the allylated alcohol **5.172** (31.6 mg, 72.0 μmol, 80%, diastereomeric mixture) as colorless oil. **R_f** = 0.37 (SiO_2, pentane/Et_2O 30:1); **FTIR (neat):** $\tilde{\nu}$ = 2958, 2930, 2857, 1741, 1643, 1463, 1368, 1233, 1133, 1020, 915, 835, 773, 665, 628, 547 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.78 – 5.68 (m, 2H), 5.54 – 5.41 (m, 2H), 5.09 – 5.01 (m, 4H), 3.79 – 3.66 (m, 2H), 3.15 – 3.00 (m, 2H), 2.60 – 2.51 (m, 2H), 2.37 – 2.27 (m, 2H), 2.22 – 2.14 (m, 4H), 2.00 (s, 3H), 2.00 (s, 3H), 1.77 –

1.62 (m, 2H), 1.54 – 1.22 (m, 13H), 1.11 – 1.07 (m, 10H), 1.01 – 0.95 (m, 15H), 0.89 – 0.87 (m, 18H), 0.05 – 0.02 (m, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 170.2, 170.1, 170.1, 147.5, 147.4, 147.1, 137.8, 137.5, 137.5, 137.3, 134.9, 134.9, 134.9, 117.3, 117.3, 117.2, 70.5, 70.4, 70.1, 70.0, 69.2, 69.0, 68.8, 68.7, 50.8, 50.7, 50.6, 50.6, 41.7, 41.4, 41.0, 40.9, 40.8, 40.7, 40.6, 40.4, 40.4, 36.5, 36.3, 36.0, 35.8, 29.9, 28.1, 28.1, 28.0, 27.9, 27.8, 27.7, 27.6, 27.6, 27.4, 27.1, 26.2, 26.1, 25.8, 24.1, 24.1, 24.0, 24.0, 21.7, 21.6, 21.6, 21.5, 21.4, 21.4, 21.4, 21.4, 21.3, 21.3, 21.2, 21.1, 21.1, 21.0, 18.3, 18.3, 1.2, -4.2, -4.3, -4.4, -4.5, -4.5; **HRMS (ESI)** m/z calcd for $C_{26}H_{48}O_3SiNa$ $[M+Na]^+$: 459.3265, found: 459.3267.

8 Appendices

8.1 List of Abbreviations, Acronyms and Symbols

(g)	gas
°C	degrees centigrade
3.5-DMP	3.5-dimethylpyrazole
9-BBN	9-borabicyclo[3.3.1]nonane
Å	Ångström
Ac	acetyl
Ac_2O	acetic anhydride
acac	acetylacetone
AChE	acetylcholinesterase
ACN	acetonitrile
AcOH	acetic acid
ACP	acyl-carrier protein
AD-mix	asymmetric dihydroxylation mixture
ADS	amorphadiene synthase
AIBN	2,2′-azobis(2-methylpropionitrile)
AIDS	acquired immune deficiency syndrome
ALS	amyotrophic lateral sclerosis
aq.	aqueous
BHT	butylated hydroxytoluene (dibutylhydroxytoluene)
brsm	based on recovered starting material
BSA	bis(trimethylsilyl)acetamide
BTPP	*tert*-butyl-imino-tri(pyrrolidino)phosphorane
Bu	butyl
Bz	benzoyl
c	concentration
calcd	calculated

CAN	ceric ammonium nitrate
cat.	catalyst or catalytic
CBS	Corey-Bakshi-Shibata
CDI	1,1'-carbonyldiimidazole
cGMP	cyclic guanosine monophosphate
CoA	coenzyme A
Cp	cyclopentadienyl
D	deuterium
d	doublet or day(s)
d.r.	diastereomeric ratio
Da	dalton(s)
DAN	2,3-diaminonaphthalene
DAST	(diethylamino)sulfur trifluoride
DATMP	diethylaluminium 2,2,6,6-tetramethylpiperidide
DBU	1,8-diazabicyclo[5.4.0]undec-7-en
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMAPP	dimethylallyl pyrophosphate
DMDO	dimethyldioxirane
DME	dimethoxyethane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DPPA	diphenyl phosphoryl azide
DU145	human prostate cancer cell
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDTA	ethylenediaminetetraacetic acid

ee	enantiomeric excess
EI	electron impact ionization
eq.	equivalent
ESI	electrospray ionization
Et	ethyl
Et_2O	diethylether
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
FDA	Food and Drug Administration
Fmoc	fluorenylmethyloxycarbonyl
FPP	farnesyl pyrophosphate
FTIR	Fourier transform infrared spectroscopy
g	gram(s)
GABA	*gamma*-aminobutyric acid
GC	gas chromatography
GSH	glutathione
h	hour(s)
ham	human antifungal metabolite
Hantzsch ester	diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate
HATU	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HCl	hydrochloric acid
HDAC	histone deacetylase
HeLa	immortal cell line
HL-60	human myeloid leukemia
HMG-CoA reductase	3-hydroxy-3-methyl-glutaryl-coenzyme A reductase
HMPA	hexamethylphosphoramide
HNO	nitroxyl
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry

HSQC	heteronuclear single quantum coherence
HWE	Horner-Wadsworth-Emmons
Hz	hertz [s^{-1}]
hn	light
IBX	2-iodoxybenzoic acid
IC_{50}	50% inhibition concentration
IEDDA	inverse-electron-demanding Diels-Alder
Imid.	imidazole
IPP	isopentenyl pyrophosphate
^{i}Pr	isopropyl
J	coupling constant
Jones reagent	sulfuric acid-chromium trioxide mixture
KHMDS	potassium bis(trimethylsilyl)amide
L-selectride	lithium-tri-*sec*-butylborohydride
LAB	lithium aminoborohydride ($LiBH_3NR_2$)
LD_{50}	50% lethale dosis
LDA	lithium diisopropylamide
LiTMP	lithium 2,2,6,6-tetramethylpiperidide
LTBA	tri-*tert*-butoxyaluminium hydride
M	molarity (mol/L)
m	multiplet
m-CPBA	*meta*-chloroperoxybenzoic acid
M.p.	melting point
MAPK	mitogen-activated protein kinase
Me	methyl
MeOH	methanol
mg	milligram(s)
min	minute(s)
mM	millimolar
mmol	millimole
MPM	4-methoxybenzyl
Ms	mesyl
MS	molecular sieve
n.d.	not determined

NADPH	nicotinamide adenine dinucleotide phosphate
NaHMDS	sodium bis(trimethylsilyl)amide
NAT	1-[H]-naphthotriazole
NCS	*N*-chlorosuccinimide
NfF	nonafluorobutane sulfonyl fluoride
NGF	nerve growth factor
NIS	*N*-iodosuccinimide
nmol	nanometer(s)
nM	nanomolar
nm	nanomole
NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance spectroscopy
NOESY	nuclear Overhauser effect spectroscopy
NOS	nitric oxide synthase
NRPS	nonribosomal peptide synthase
p-TsOH	*p*-toluenesulfonic acid
P.	Plasmodium
PABA	*p*-aminobenzoate
PC12	cell line (rat adrenal gland phaeochromocytoma)
PCC	pyridinium chlorochromate
$Pd(quinox)Cl_2$	dichloro[2-(4,5-dihydro-2 oxazolyl)quinoline]palladium(II)
Petasis reagent	Cp_2TiMe_2
Ph	phenyl
pH	potential hydrogen
PHABA	*p*-hydroxylaminobenzoate
PhH	toluene
PIDA	(diacetoxyiodo)benzene
PMP	*p*-methoxyphenyl
PNBA	*p*-nitrobenzoate
PPh_3	triphenylphospine
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate

proton sponge	1,8-bis(dimethylamino)naphthalene, *N*,*N*,*N*′,*N*′-tetramethyl-1,8-naphthalenediamine
py	pyridine
q	quartet
quant.	quantitative
r.t.	room temperature
RCM	ring closing metathesis
Red-Al	sodium bis(2-methoxyethoxy)aluminumhydride
R_f	retention factor
RNI	reactive nitrogen intermediates
ROS	reactive oxygen species
s	singlet
SAHA	suberoylanilide hydroxamic acid
SAR	structure-activity relationship
SET	single electron transfer
SH-SY5Y	neuroblast from neural tissue
SI	selectivity index
S_N1	unimolecular nucleophilic substitution
S_N2	bi-molecular nucleophilic substitution
S_N2'	bi-molecular nucleophilic conjugate substitution
SOMO	single occupied molecular orbital
super-hydride	lithium triethylborohydride
t	triplet
t-BuOOH	*tert*-butylhydroperoxide
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butylhydroperoxide
TBS	*tert*-butyldimethylsilyl
TBTU	*O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate
TEMPO	2,2,6,6-tetramethylpiperidin-1-yloxy
TESOTf	trimethylsilyl trifluoromethanesulfonate
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid

THF	tetrahydrofuran
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMS	trimethylsilyl
TosMIC	*p*-toluenesulfonylmethyl isocyanide
TPAP	tetrapropylammonium perruthenate
Ts	tosyl
WHO	World Health Organization
δ	chemical shift
μM	micromolar
μmol	micromole

8.2 Crystal Structures

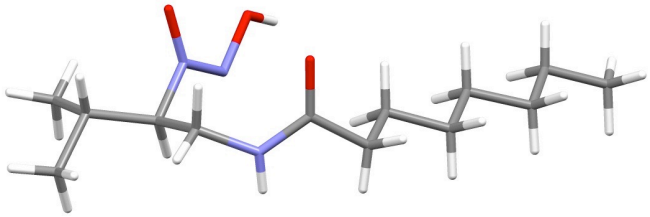


Table 8.1: Crystal data for **2.80a.**

formula	$C_{13}H_{27}N_3O_3$
formula weight	273.38
Z, calculated density	4, 1.145 Mg · m^{-3}
F(000)	600
description and size of crystal	colourless block, 0.050 · 0.110 · 0.190 mm^3
absorption coefficient	0.660 mm^{-1}
min/max transmission	0.93 / 0.97
temperature	123K
radiation(wavelength)	Cu K_α (λ = 1.54178 Å)
Crystal system, space group	orthorhombic, P 2_1 2_1 2_1
a	5.6786(4) Å
b	9.1130(6) Å
c	30.633(2) Å
α	90°
β	90°
γ	90°
V	1585.26(19) $Å^3$
min/max Θ	5.063° / 68.828°
number of collected reflections	19332
number of independent reflections	2887 (merging r = 0.036)
number of observed reflections	2847 (I>2.0σ(I))
number of refined parameters	173
r	0.0290
rW	0.0241
goodness of fit	0.9594

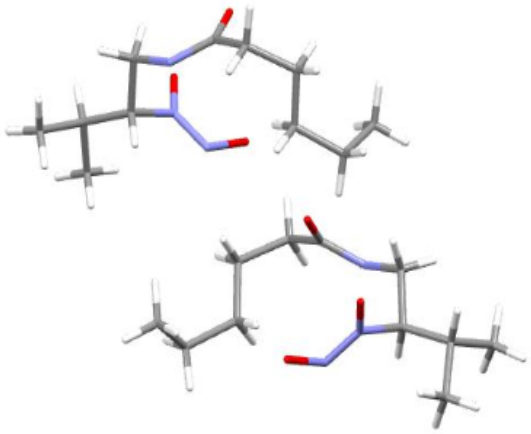


Table 8.2: Crystal data for **2.140a**.

formula	$C_{11}H_{21}N_3O_3$
formula weight	243.31
Z, calculated density	2, 1.144 Mg · m^{-3}
F(000)	263.998
description and size of crystal	colourless block, 0.030 · 0.070 · 0.190 mm^3
absorption coefficient	0.689 mm^{-1}
min/max transmission	0.95 / 0.98
temperature	123K
radiation(wavelength)	Cu K_α (λ = 1.54180 Å)
Crystal system, space group	triclinic, P 1
a	5.9207(7) Å
b	10.1597(12) Å
c	11.7692(15) Å
α	87.404(9)°
β	87.059(7)°
γ	89.796(7)°
V	1706.29(9) $Å^3$
min/max Θ	3.764° / 68.514°
number of collected reflections	10810
number of independent reflections	4617 (merging r = 0.048)
number of observed reflections	3916 (I>2.0σ(I))
number of refined parameters	308
r	0.1030
rW	0.1253
goodness of fit	1.0499

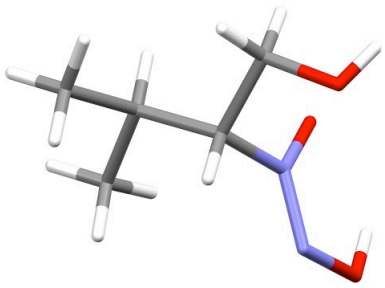


Table 8.3: Crystal data for (–)-valdiazen (**2.105a**).

formula	$C_5H_{12}N_2O_3$
formula weight	148.17
Z, calculated density	4, 1.276 Mg · m^{-3}
F(000)	320
description and size of crystal	colourless plate, 0.03 · 0.22 · 0.22 mm^3
absorption coefficient	0.890 mm^{-1}
min/max transmission	0.62289 / 1.00000
temperature	160(2)K
radiation(wavelength)	Cu K_α (λ = 1.54184 Å)
Crystal system, space group	???, ???
a	6.14476(18) Å
b	9.3078(3) Å
c	13.4817(5) Å
α	90°
β	90°
γ	90°
V	771.08(5) $Å^3$
min/max Θ	5.776° / 74.175°
number of collected reflections	7248
number of independent reflections	1558 (merging r = 0.0715)
number of observed reflections	1558 (I > 2σ(I))
number of refined parameters	101
r	0.0379
rW	0.0999
goodness of fit	1.042

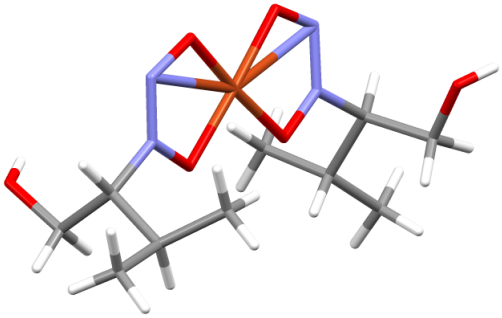


Table 8.4: Crystal data for Cu-valdiazen (**2.145**).

formula	$C_{10}H_{22}Cu\,N_4O_6$
formula weight	357.85
Z, calculated density	2, 1.556 Mg · m^{-3}
F(000)	374
description and size of crystal	blue prism, 0.08 · 0.11 · 0.25 mm^3
absorption coefficient	1.461 mm^{-1}
min/max transmission	0.89316 / 1.00000
temperature	160(2)K
radiation(wavelength)	Mo K_α (λ = 0.71073 Å)
Crystal system, space group	???, ???
a	9.39300(15) Å
b	6.89236(11) Å
c	11.95735(18) Å
α	90°
β	99.2698(15)°
γ	90°
V	764.01(2) $Å^3$
min/max Θ	2.197° / 30.517°
number of collected reflections	18905
number of independent reflections	4261 (merging r = 0.0289)
number of observed reflections	4261 (I > 2σ(I))
number of refined parameters	202
r	0.0230
rW	0.0530
goodness of fit	1.041

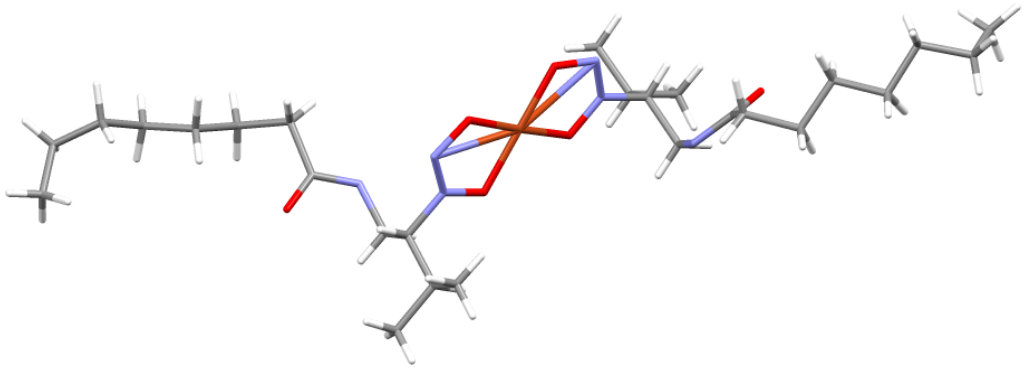


Table 8.5: Crystal data for Cu-fragin (**2.144**).

formula	$C_{26}H_{50}Cu_1N_6O_6$
formula weight	606.27
Z, calculated density	3, 1.234 Mg · m^{-3}
F(000)	975.000
description and size of crystal	blue needle, 0.030 · 0.040 · 0.190 mm^3
absorption coefficient	1.312 mm^{-1}
min/max transmission	0.95 / 0.96
temperature	123K
radiation(wavelength)	Cu K_α (λ = 1.54178 Å)
Crystal system, space group	trigonal, P 3_2 2 1
a	14.3908(18) Å
b	14.3908(18) Å
c	13.6423(18) Å
α	90°
β	90°
γ	120°
V	2446.7(3) $Å^3$
min/max Θ	3.546° / 68.667°
number of collected reflections	23414
number of independent reflections	3010 (merging r = 0.042)
number of observed reflections	2886 (I>2.0σ(I))
number of refined parameters	242
r	0.0635
rW	0.0764
goodness of fit	1.0153

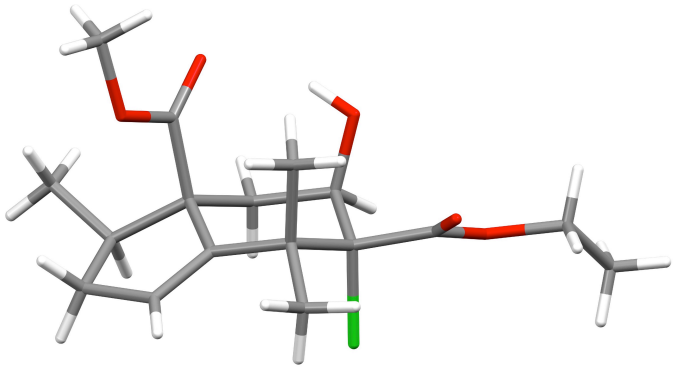


Table 8.6: Crystal data for **3.143**.

CCDC	1478756
Formula	$C_{17}H_{25}Cl_1O_5$
formula weight	344.83
Z, calculated density	4, 1.312 Mg · m^{-3}
F(000)	736
description and size of crystal	colourless block, 0.110 · 0.170 · 0.250 mm^3
absorption coefficient	2.132 mm^{-1}
min/max transmission	0.70 / 0.79
temperature	123K
radiation(wavelength)	Cu K_α (λ = 1.54178 Å)
Crystal system, space group	orthorhombic, $P\,2_1\,2_1\,2_1$
a	7.6753(6) Å
b	9.7959(7) Å
c	23.2215(17) Å
α	90°
β	90°
γ	90°
V	1745.94(13) $Å^3$
min/max Θ	4.900° / 68.960°
number of collected reflections	8802
number of independent reflections	3112 (merging r = 0.032)
number of observed reflections	3031 (I>2.0σ(I))
number of refined parameters	209
r	0.0260
rW	0.0298
goodness of fit	1.0925

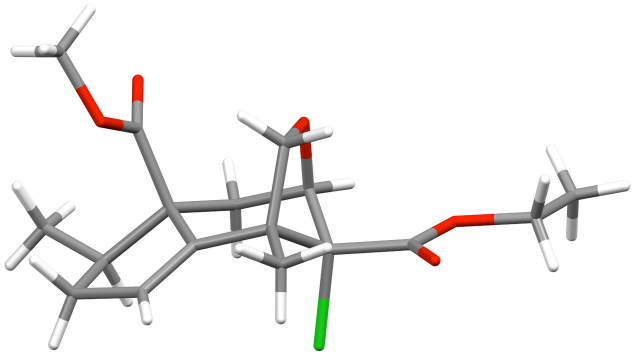


Table 8.7: Crystal data for **3.144**.

CCDC	1478757
formula	$C_{17}H_{23}Cl_1O_5$
formula weight	342.82
Z, calculated density	2, 1.327 Mg · m^{-3}
F(000)	364
description and size of crystal	colourless block, 0.020 · 0.110 · 0.140 mm^3
absorption coefficient	2.168 mm^{-1}
min/max transmission	0.79 / 0.96
temperature	123K
radiation(wavelength)	Cu K_α (λ = 1.54178 Å)
Crystal system, space group	monoclinic, $P\,2_1$
a	10.6723(7) Å
b	7.1954(4) Å
c	11.9267(8) Å
α	90°
β	110.456(4)°
γ	90°
V	858.11(6) $Å^3$
min/max Θ	4.422° / 68.888°
number of collected reflections	6396
number of independent reflections	2940 (merging r = 0.030)
number of observed reflections	2628 (I>2.0σ(I))
number of refined parameters	209
r	0.0413
rW	0.0487
goodness of fit	1.0949

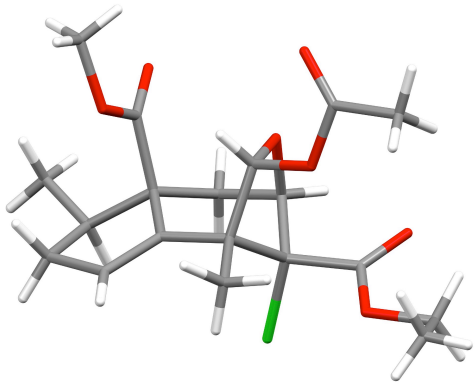


Table 8.8: crystal data for **3.145**.

CCDC	1478759
formula	$C_{19}H_{25}Cl_1O_7$
formula weight	400.86
Z, calculated density	4, 1.334 Mg · m^{-3}
F(000)	847.995
description and size of crystal	colourless plate, 0.020 · 0.110 · 0.180 mm^3
absorption coefficient	2.022 mm^{-1}
min/max transmission	0.80 / 0.96
temperature	123K
radiation(wavelength)	Cu K_α (λ = 1.54178 Å)
Crystal system, space group	orthorhombic, $P\,2_1\,2_1\,2_1$
a	7.1620(5) Å
b	12.0359(8) Å
c	23.1600(14) Å
α	90°
β	90°
γ	90°
V	1996.42(12) $Å^3$
min/max Θ	3.817° / 69.292°
number of collected reflections	23952
number of independent reflections	3699 (merging r = 0.039)
number of observed reflections	3338 (I>2.0σ(I))
number of refined parameters	245
r	0.0277
rW	0.0333
goodness of fit	1.0976

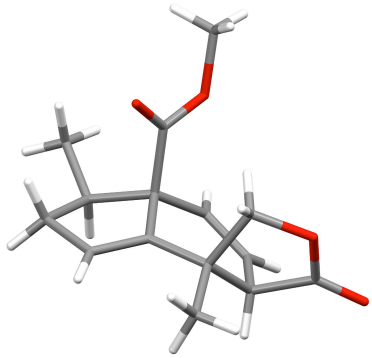


Table 8.9: Crystal data for **3.164.**

CCDC	1478760
formula	$C_{15}H_{18}O_4$
formula weight	262.31
Z, calculated density	4, 1.299 Mg · m^{-3}
F(000)	560
description and size of crystal	colourless plate, 0.020 · 0.170 · 0.250 mm^3
absorption coefficient	0.768 mm^{-1}
min/max transmission	0.88 / 0.98
temperature	123K
radiation(wavelength)	Cu K_α (λ = 1.54178 Å)
Crystal system, space group	orthorhombic, P 2_1 2_1 2_1
a	6.6415(5) Å
b	8.3791(6) Å
c	24.1022(17) Å
α	90°
β	90°
γ	90°
V	1341.28(9) $Å^3$
min/max Θ	3.668° / 68.824°
number of collected reflections	8778
number of independent reflections	2351 (merging r = 0.039)
number of observed reflections	2123 (I>2.0σ(I))
number of refined parameters	173
r	0.0272
rW	0.0307
goodness of fit	1.1332

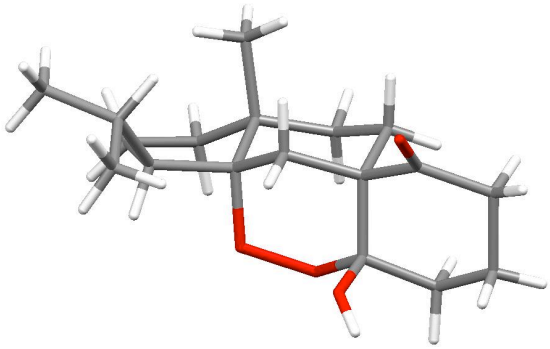


Table 8.10: Crystal data for **4.49.**

CCDC	914565
formula	$C_{18}H_{28}O_4$
formula weight	308.42
Z, calculated density	8, 1.287 Mg · m^{-3}
F(000)	1344
description and size of crystal	colorless plate, 0.030 · 0.110 · 0.320 mm^3
absorption coefficient	0.089 mm^{-1}
min/max transmission	0.99 / 1.00
temperature	123K
radiation(wavelength)	Mo *K*α (λ = 0.71073 Å)
Crystal system, space group	tetragonal, P 4_1 2_1 2
a	7.3830(3) Å
b	7.3830(3) Å
c	58.407(3) Å
α	90°
β	90°
γ	90°
V	3183.7(3) $Å^3$
min/max Θ	1.395° / 27.484°
number of collected reflections	12591
number of independent reflections	2311 (merging r = 0.096)
number of observed reflections	1905 (I>2.0σ(I))
number of refined parameters	199
r	0.1061
rW	0.0784
goodness of fit	1.1005

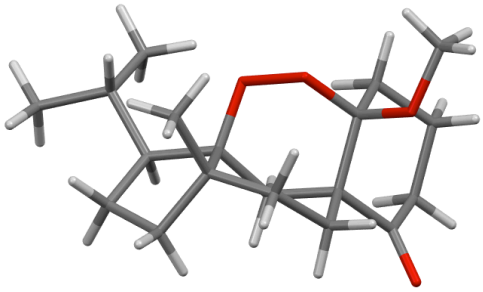


Table 8.11: Crystal data for **4.62.**

CCDC	1054561
formula	$C_{19}H_{30}O_4$
formula weight	322.44
Z, calculated density	4, 1.221 Mg · m^{-3}
F(000)	703.994
description and size of crystal	colorless needle 0.030 · 0.080 · 0.210 mm^3
absorption coefficient	0.671 mm^{-1}
min/max transmission	0.95 / 0.98
temperature	123K
radiation(wavelength)	Cu Kα (λ = 1.54178 Å)
Crystal system, space group	monoclinic, P c
a	14.9923(19) Å
b	9.5834(11) Å
c	12.5518(15) Å
α	90°
β	103.442(2)°
γ	90°
V	1754.0(2) $Å^3$
min/max Θ	3.030° / 69.128°
number of collected reflections	23344
number of independent reflections	6318 (merging r = 0.059)
number of observed reflections	6292 (I>2.0σ(I))
number of refined parameters	415
r	0.0372
rW	0.0409
goodness of fit	1.0900

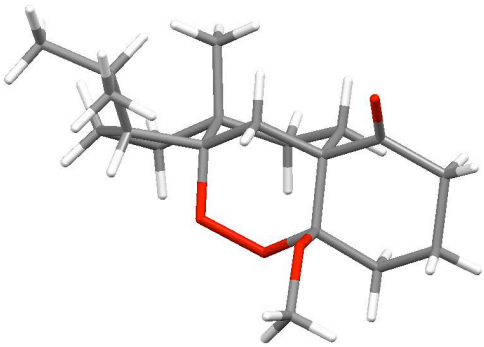
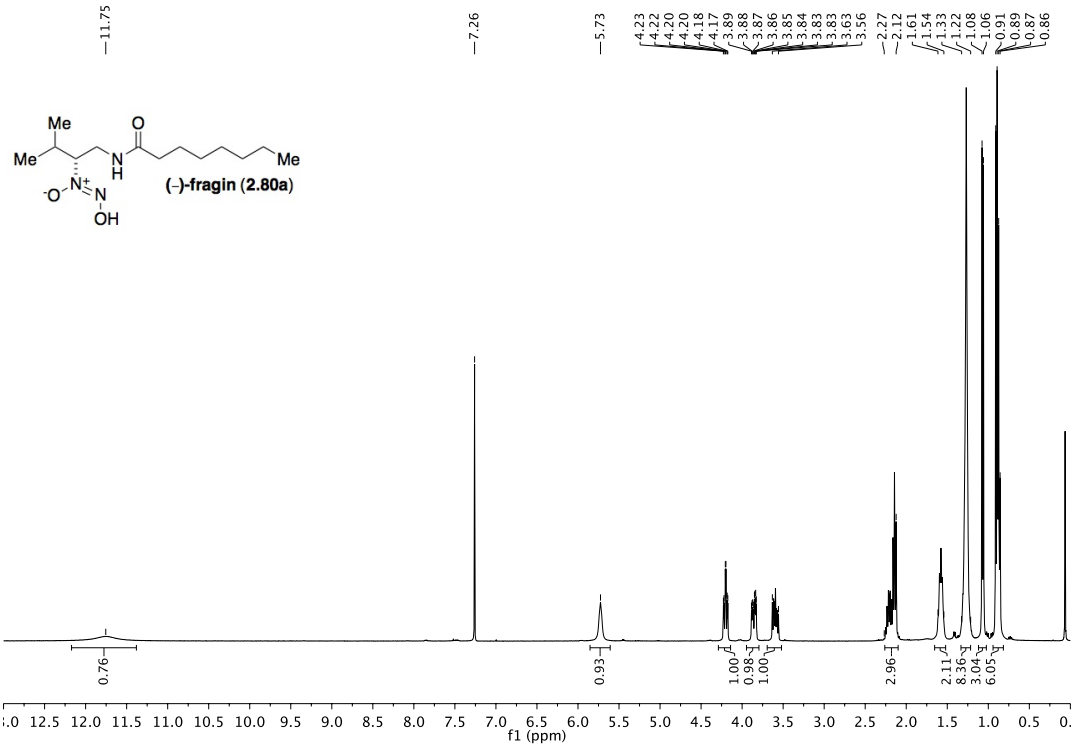


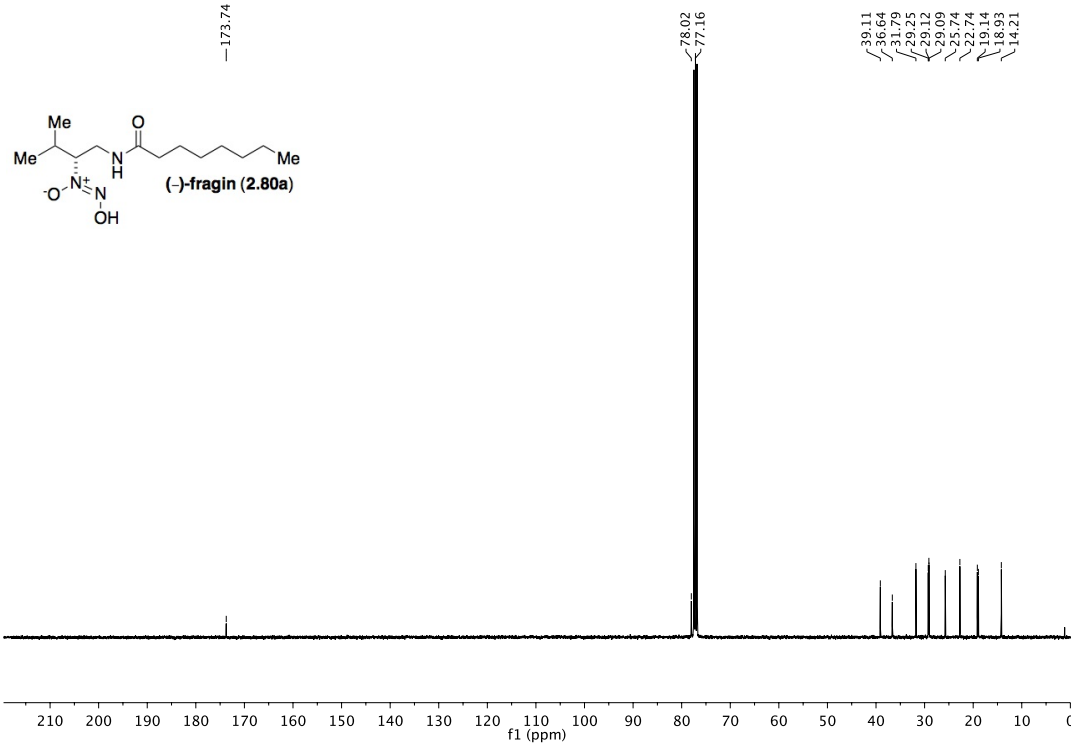
Table **8.12**:Crystal data for **4.61**.

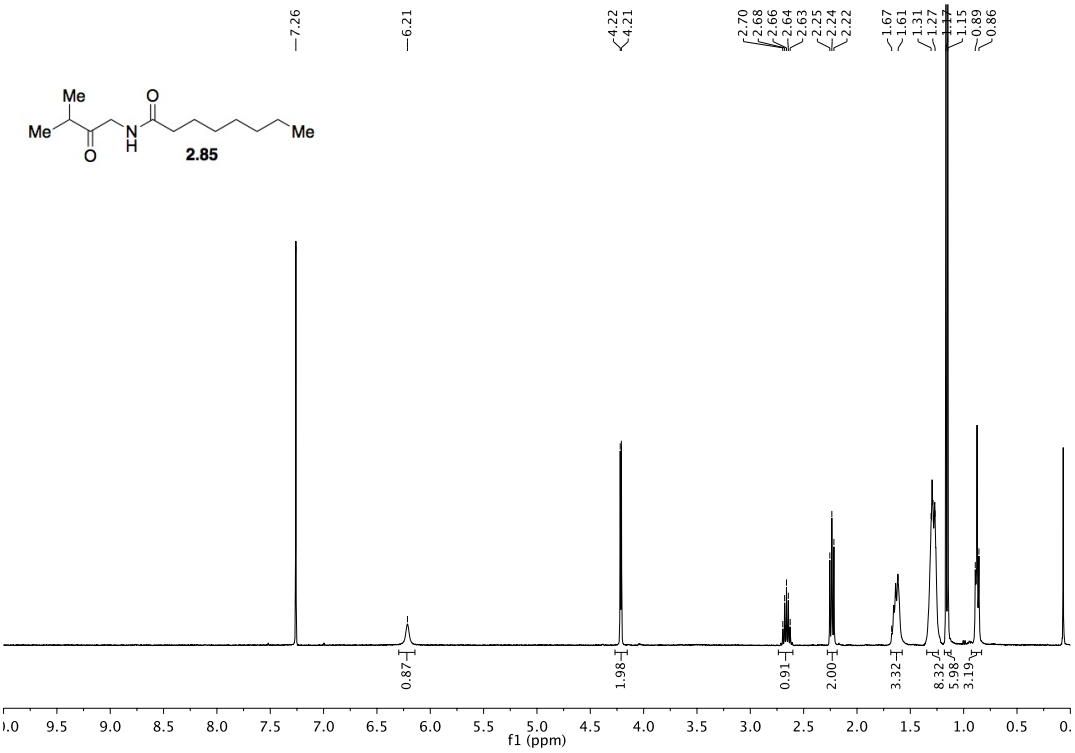
CCDC	914569
formula	$C_{19}H_{30}O_4$
formula weight	322.44
Z, calculated density	2, 1.255 Mg · m^{-3}
F(000)	352
description and size of crystal	colorless plate, 0.010 · 0.170 · 0.260 mm^3
absorption coefficient	0.086 mm^{-1}
min/max transmission	0.99 / 1.00
temperature	123K
radiation(wavelength)	Mo *K*α (λ = 0.71073 Å)
Crystal system, space group	monoclinic, P 1 2_1 1
a	7.6255(11) Å
b	7.0963(11) Å
c	15.962(2) Å
α	90°
β	99.002(9)°
γ	90°
V	853.1(2) $Å^3$
min/max Θ	2.584° / 28.289°
number of collected reflections	9053
number of independent reflections	2233 (merging r = 0.094)
number of observed reflections	2223 (I>2.0σ(I))
number of refined parameters	208
r	0.0612
rW	0.1476
goodness of fit	0.91

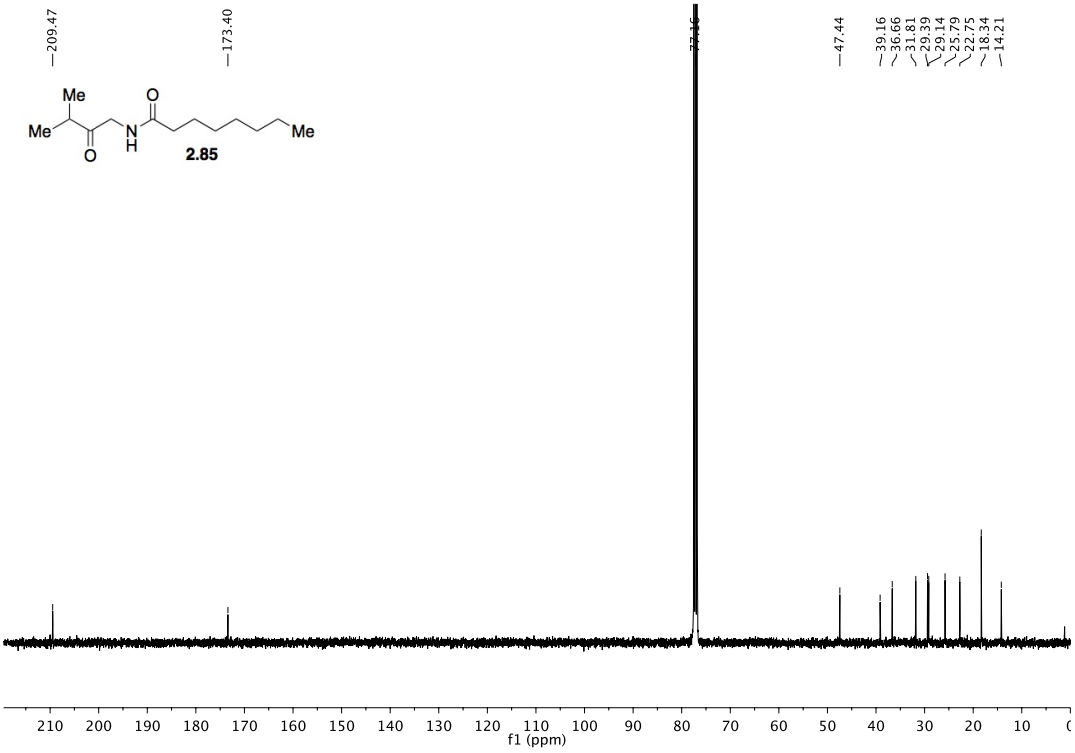
8.3 NMR-spectra

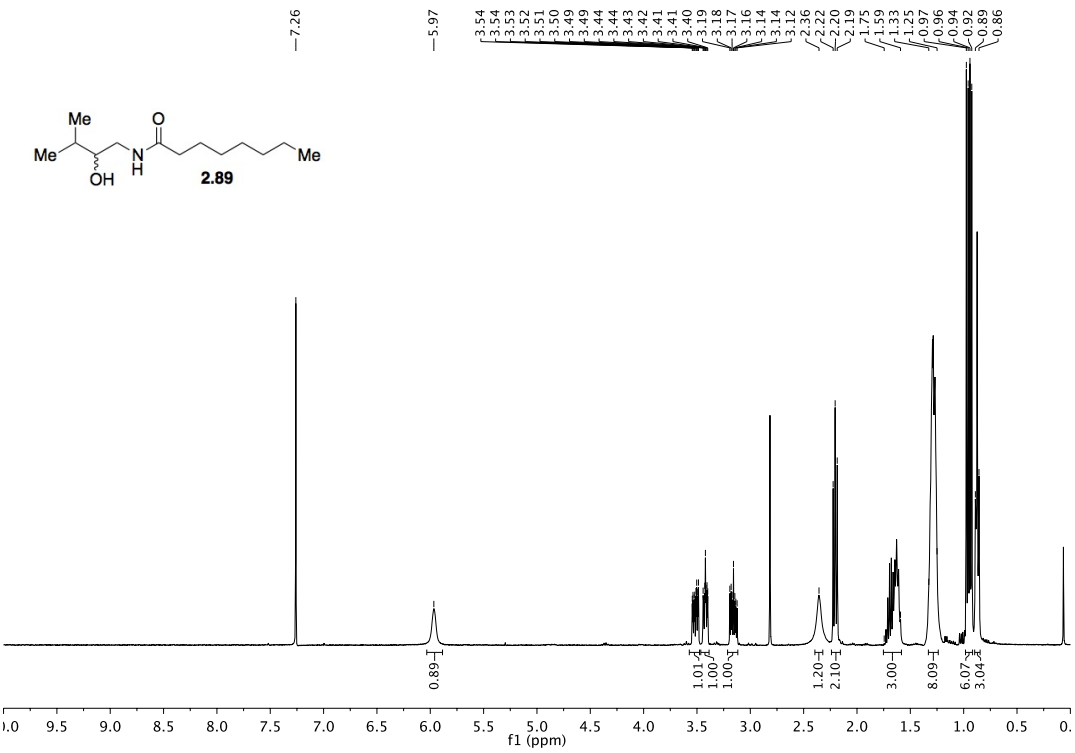
8.3.1 Total Syntheses and SAR-Studies on (–)-Fragin and Valdiazen

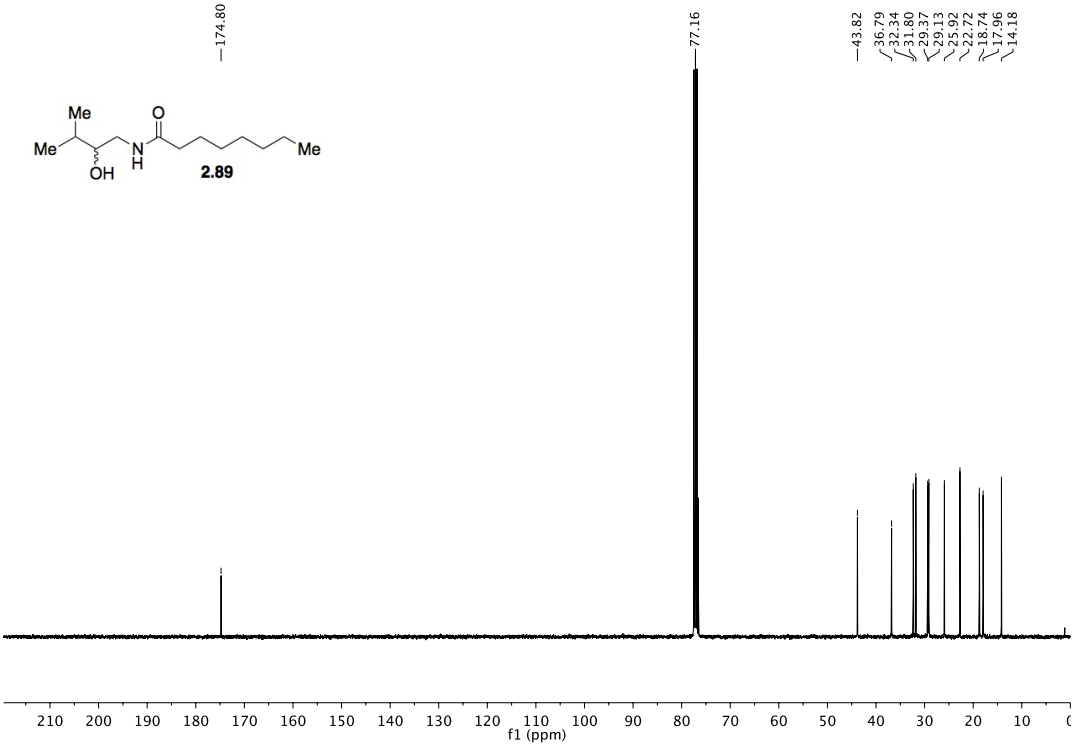





7.26
6.21
4.22
4.21
2.70
2.68
2.66
2.64
2.63
2.25
2.24
2.22
1.67
1.61
1.31
1.27
1.15
0.89
0.86
Me
O
Me
N
H
O
Me
2.85
0.87
1.98
0.91
2.00
3.32
8.32
5.98
3.19
f1 (ppm)


209.47
173.40
47.44
39.16
36.66
31.81
29.39
29.14
25.79
22.75
18.34
14.21
Me
O
Me
N
H
O
Me
2.85
f1 (ppm)


7.26
5.97
3.54
3.54
3.53
3.52
3.51
3.50
3.49
3.49
3.44
3.44
3.43
3.42
3.41
3.41
3.40
3.19
3.18
3.17
3.16
3.14
3.14
3.12
2.36
2.22
2.20
2.19
1.75
1.59
1.33
1.25
0.97
0.96
0.94
0.92
0.89
0.86
Me
Me
OH
N
H
O
Me
2.89
0.89
1.01
1.00
1.00
1.20
2.10
3.00
8.09
6.07
3.04
f1 (ppm)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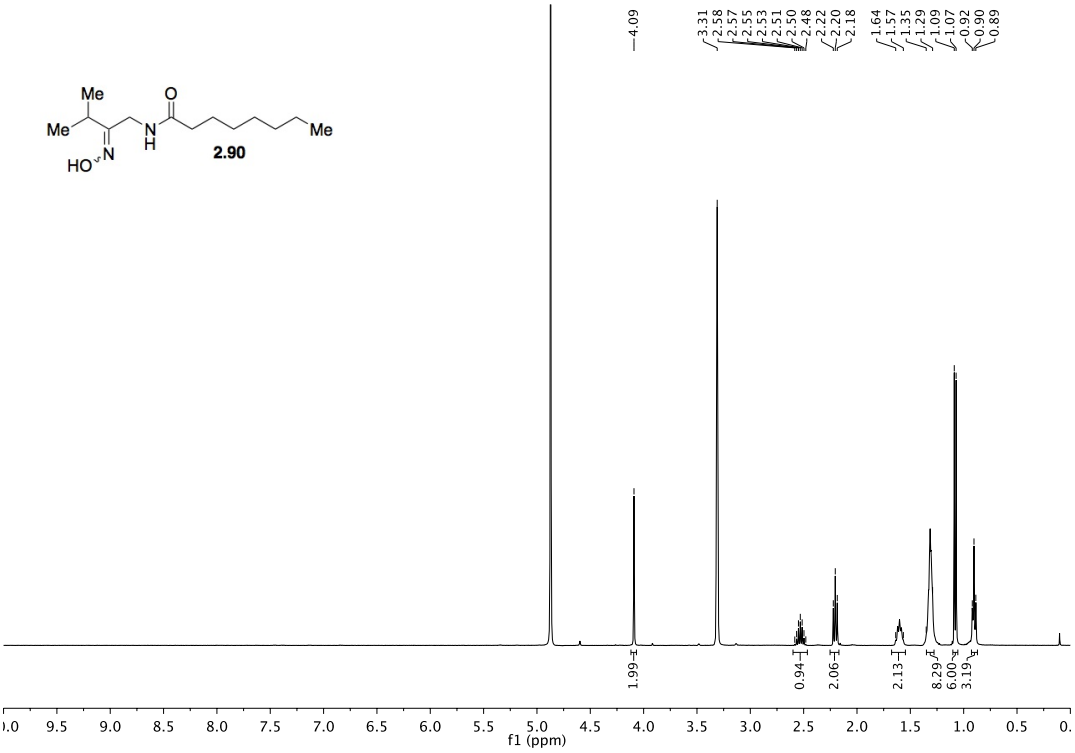
77.16
43.82
36.79
32.34
31.80
29.37
29.13
25.92
22.72
18.74
17.96
14.18
Me
Me
OH
N
H
O
Me
2.89
f1 (ppm)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Me
HO
N
O
N
H
Me
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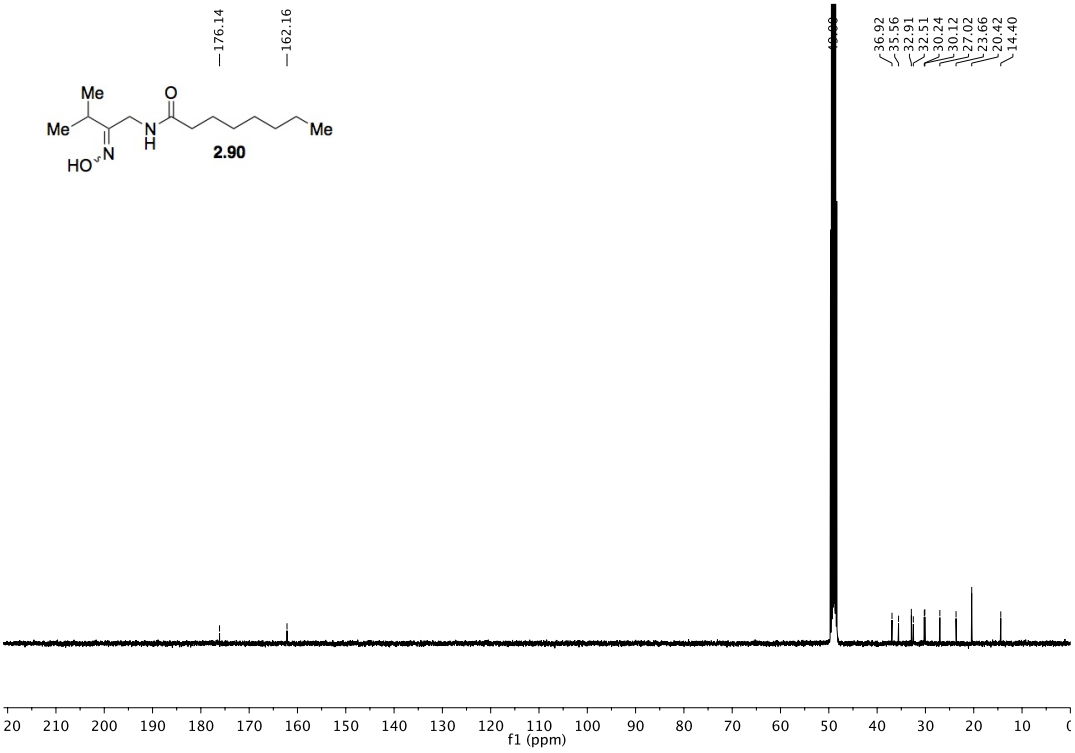
4.09
3.31
2.58
2.57
2.55
2.53
2.51
2.50
2.48
2.22
2.20
2.18
1.64
1.57
1.35
1.29
1.09
1.07
0.92
0.90
0.89
1.99
0.94
2.06
2.13
8.29
6.00
3.19
f1 (ppm)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Me
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O
N
H
Me
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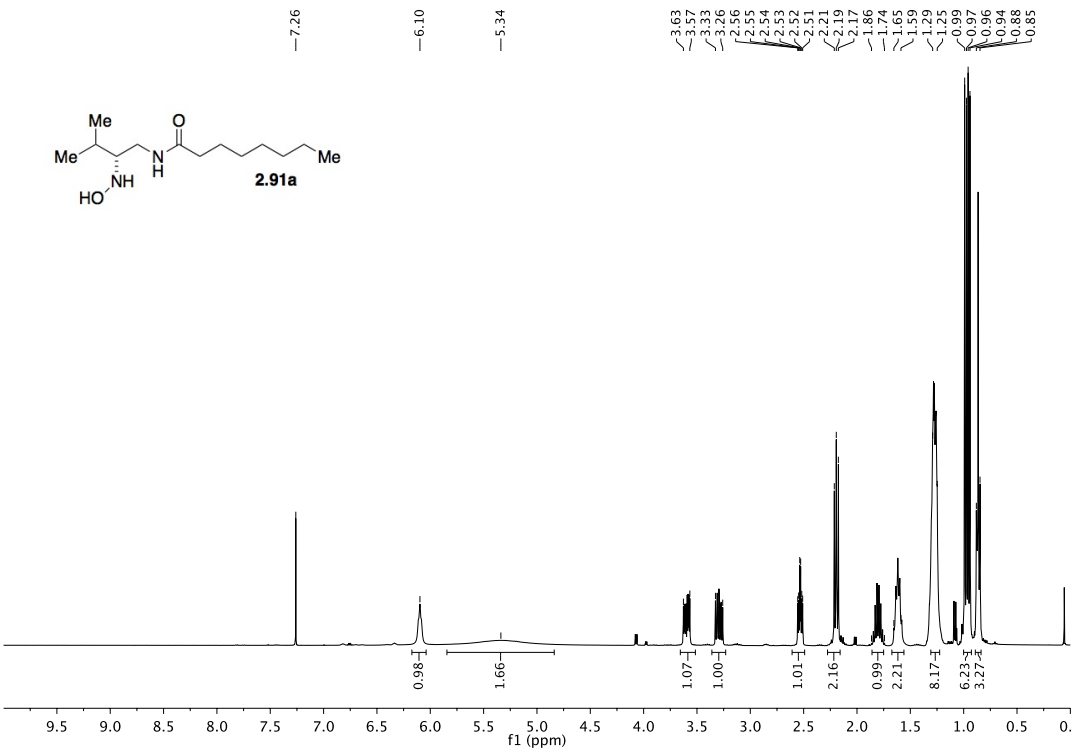
32.91
32.51
30.24
30.12
27.02
23.66
20.42
14.40
f1 (ppm)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3.33
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2.56
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2.54
2.53
2.52
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2.21
2.19
2.17
1.86
1.74
1.65
1.59
1.29
1.25
0.99
0.97
0.96
0.94
0.88
0.85
Me
Me
O
N
H
NH
HO
Me
2.91a
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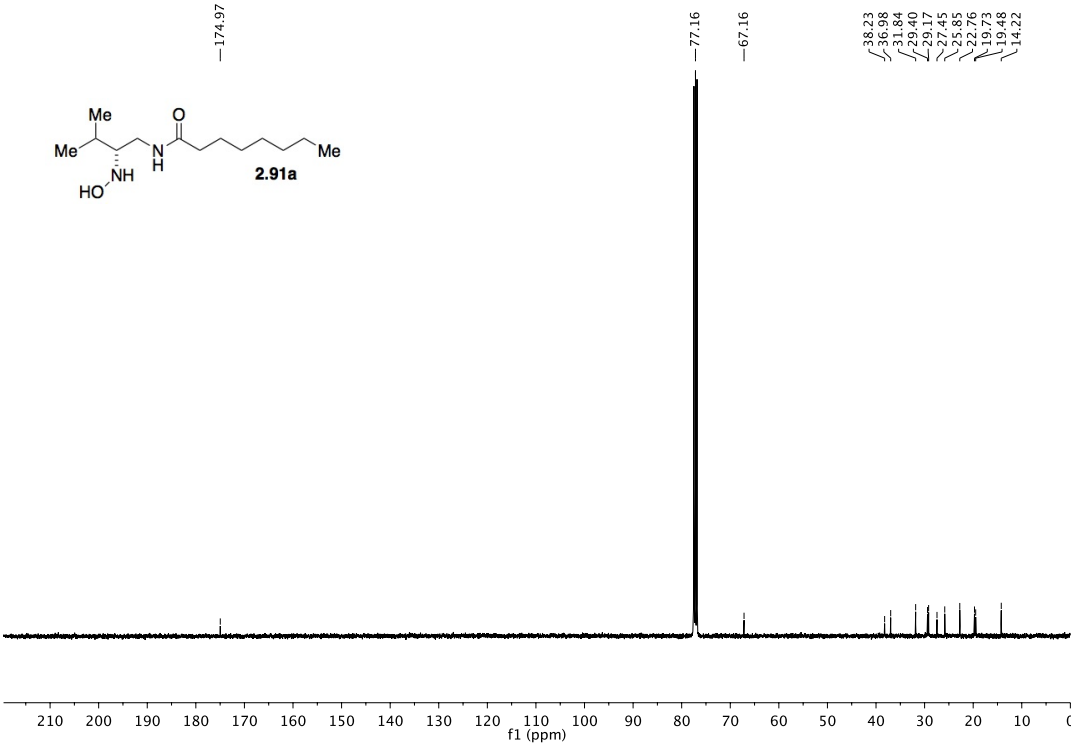
1.07
1.00
1.01
2.16
0.99
2.21
8.17
6.23
3.27
f1 (ppm)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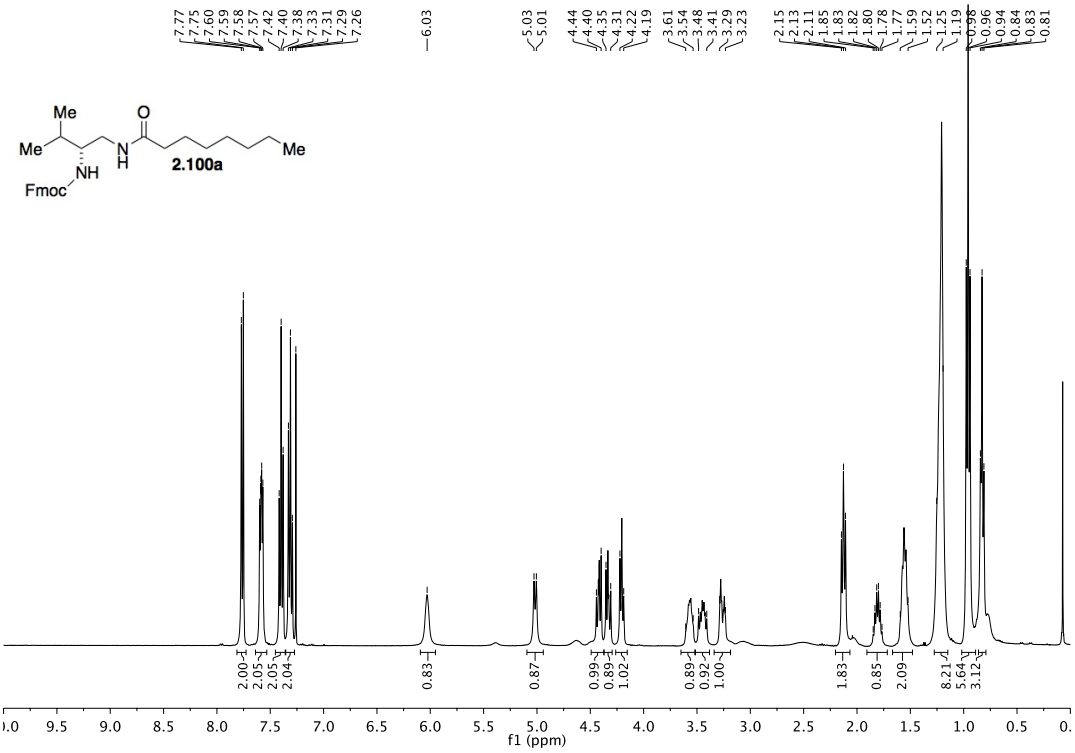
67.16
38.23
36.98
31.84
29.40
29.17
27.45
25.85
22.76
19.73
19.48
14.22
Me
Me
O
N
H
NH
HO
Me
2.91a
f1 (ppm)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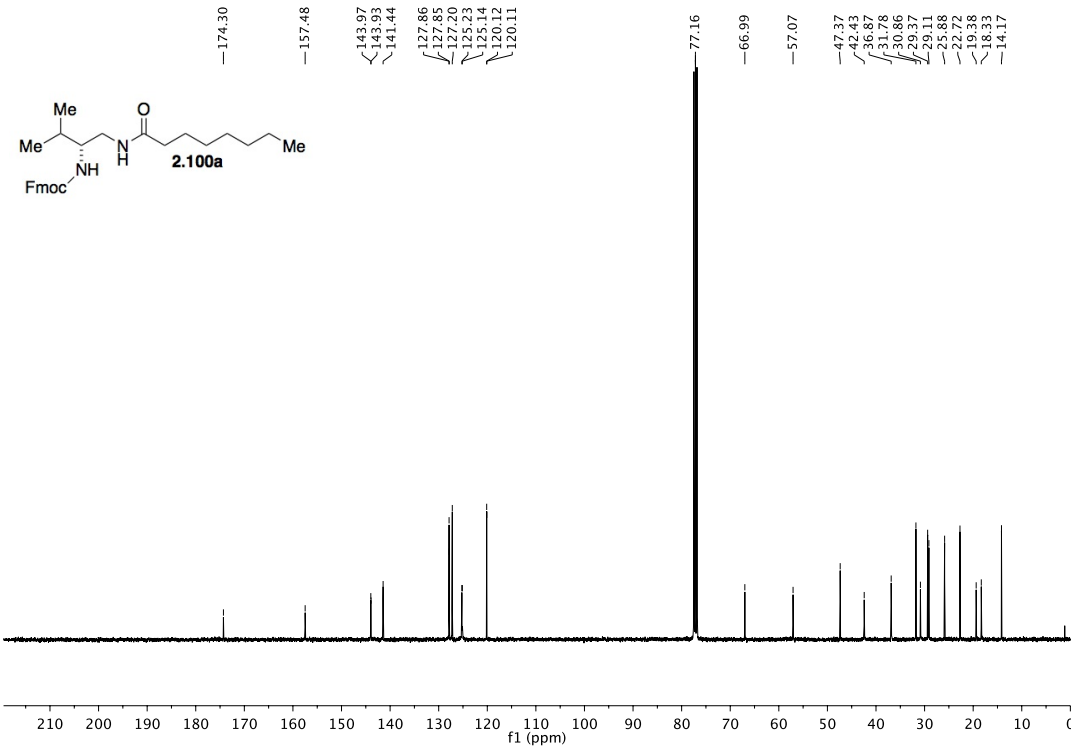
H
Me
NH
Fmoc
2.100a
f1 (ppm)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Me
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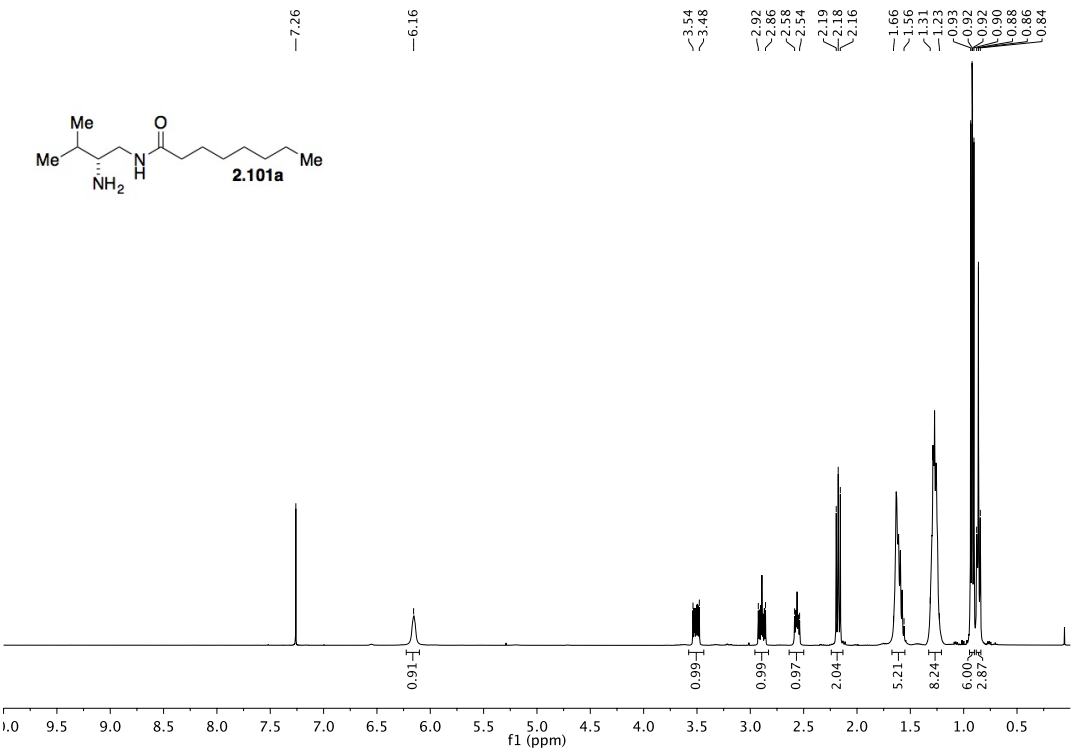
N
H
Me
NH
Fmoc
2.100a
f1 (ppm)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2.58
2.54
2.19
2.18
2.16
1.66
1.56
1.31
1.23
0.93
0.92
0.92
0.90
0.88
0.86
0.84
Me
Me
O
N
H
NH2
Me
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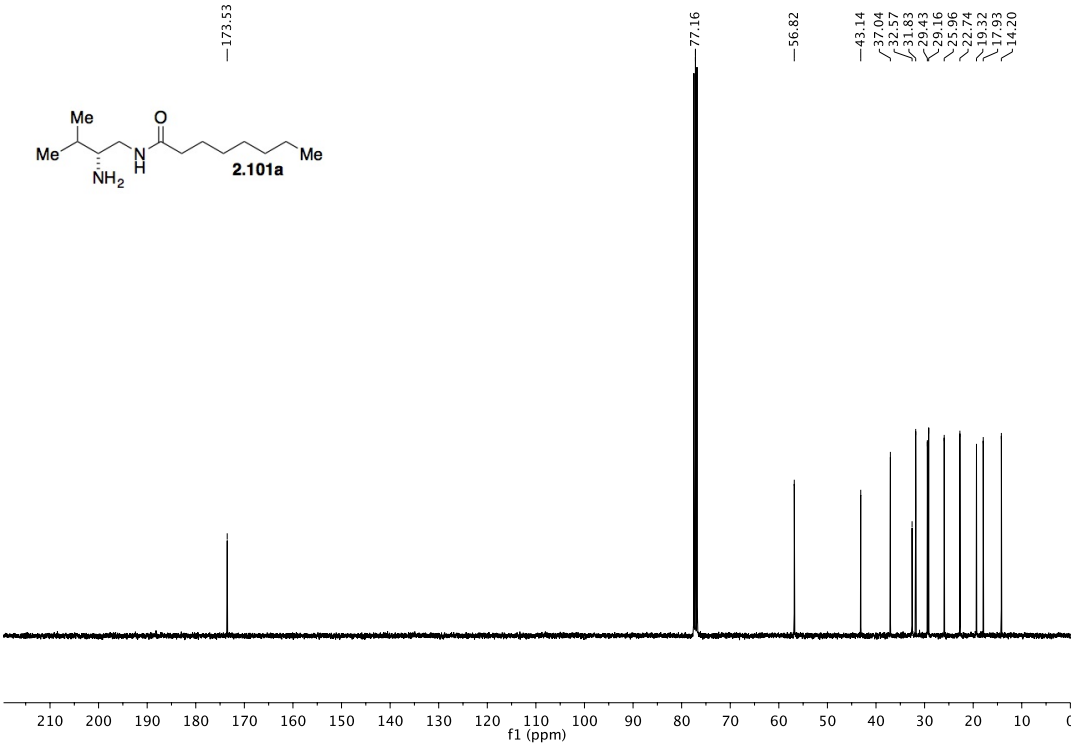
0.99
0.99
0.97
2.04
5.21
8.24
6.00
2.87
f1 (ppm)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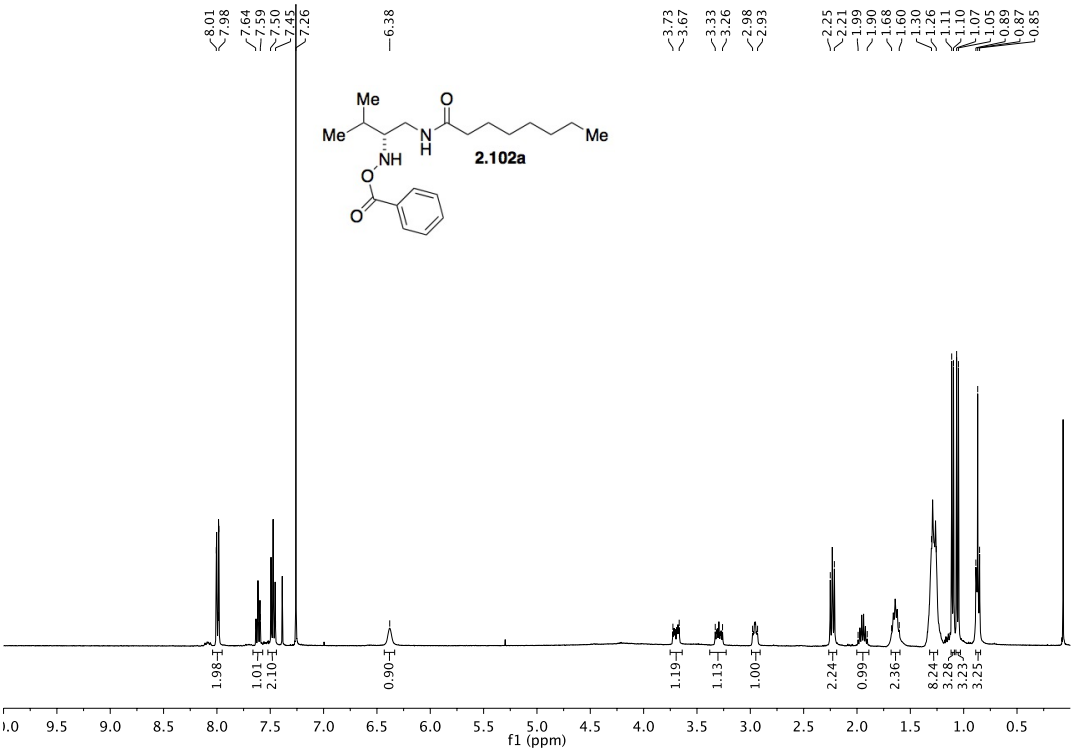
37.04
32.57
31.83
29.43
29.16
25.96
22.74
19.32
17.93
14.20
Me
Me
O
N
H
NH2
Me
2.101a
f1 (ppm)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7.98
7.64
7.59
7.50
7.45
7.26
6.38
3.73
3.67
3.33
3.26
2.98
2.93
2.25
2.21
1.99
1.90
1.68
1.60
1.30
1.26
1.11
1.10
1.07
1.05
0.89
0.87
0.85
Me
Me
N
H
O
Me
NH
O
O
2.102a
1.98
1.01
2.10
0.90
1.19
1.13
1.00
2.24
0.99
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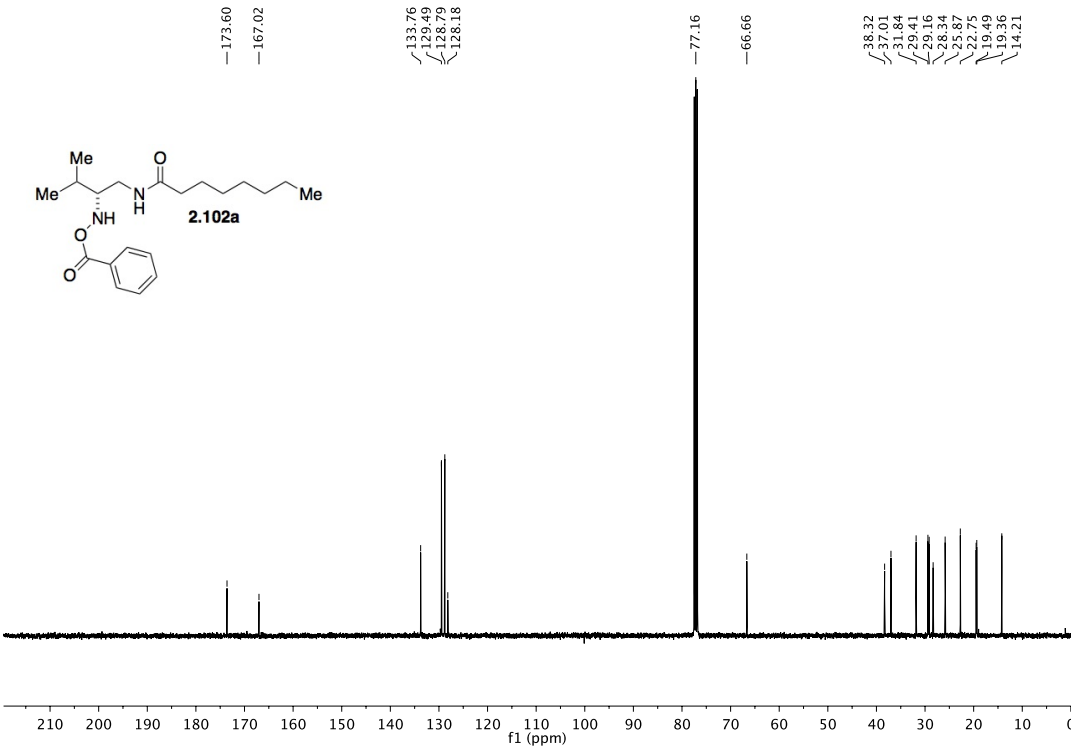
8.24
3.28
3.23
3.25
f1 (ppm)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167.02
133.76
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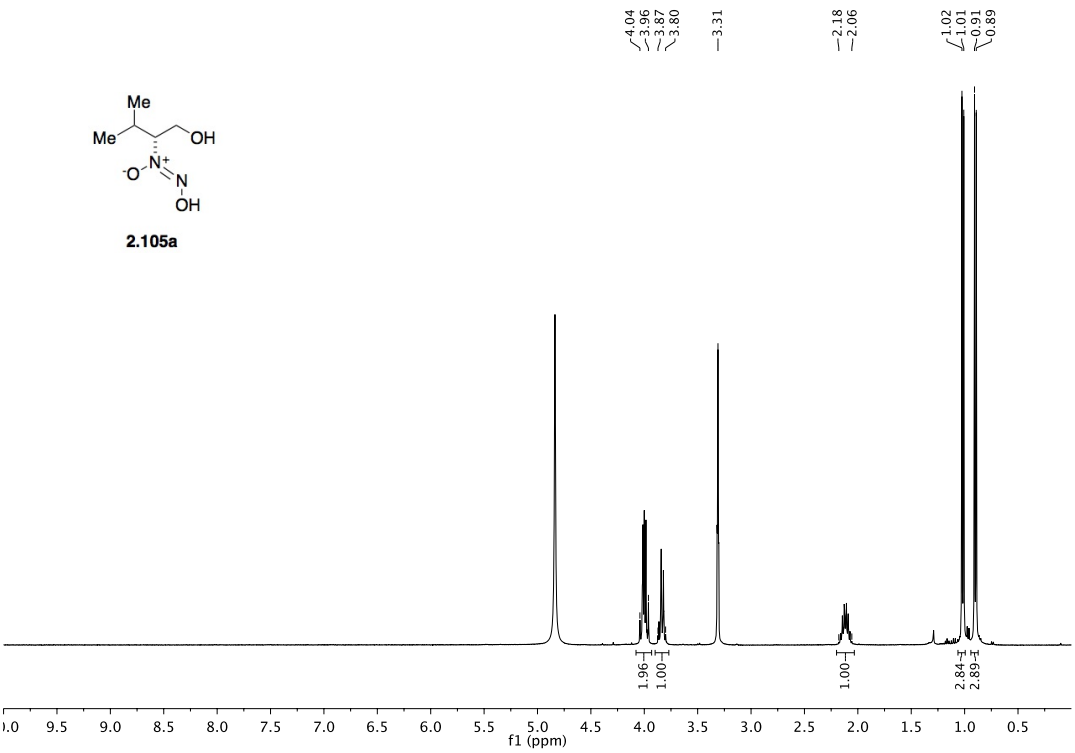
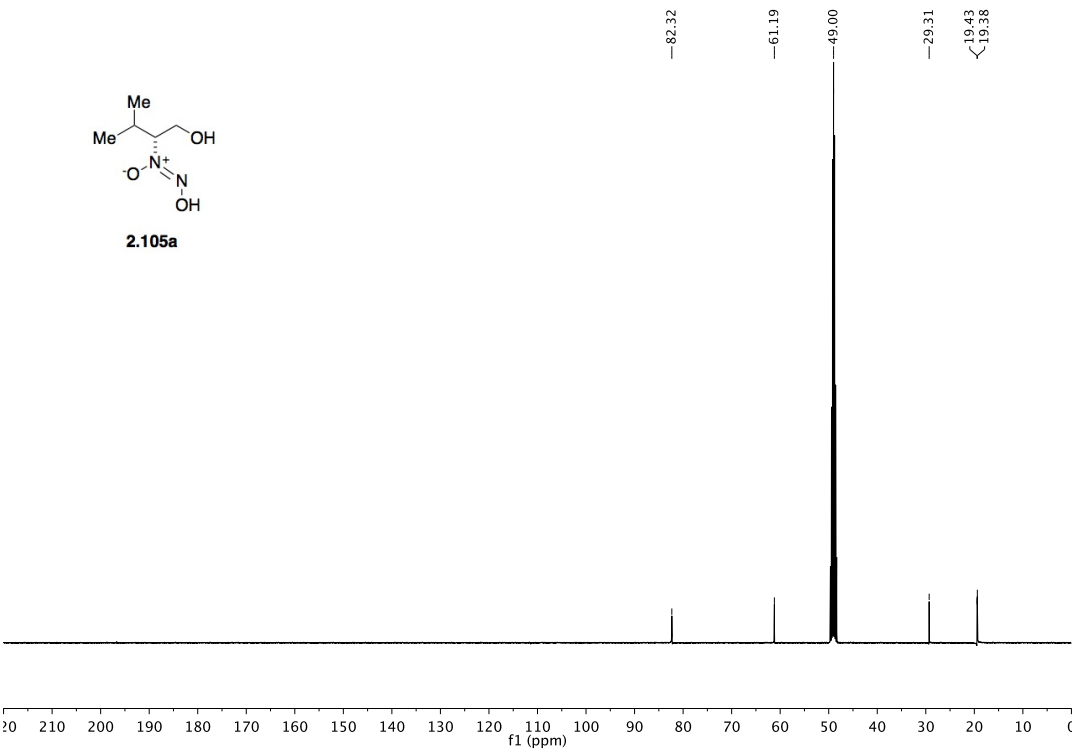
128.79
128.18
77.16
66.66
38.32
37.01
31.84
29.41
29.16
28.34
25.87
22.75
19.49
19.36
14.21
Me
Me
N
H
O
Me
NH
O
O
2.102a
f1 (ppm)


4.04
3.96
3.87
3.80
3.31
2.18
2.06
1.02
1.01
0.91
0.89
Me
Me
OH
N+
O
N
OH
2.105a
1.96
1.00
1.00
2.84
2.89
f1 (ppm)


82.32
61.19
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19.43
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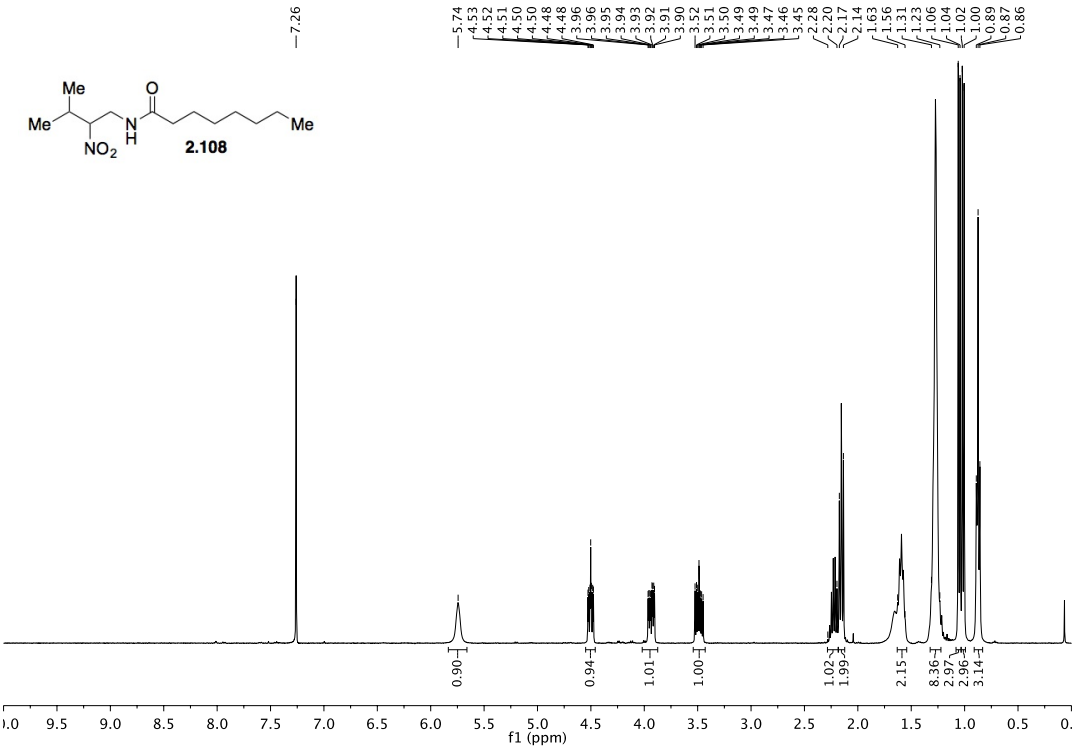
Me
Me
OH
N+
O
N
OH
2.105a
f1 (ppm)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3.96
3.95
3.94
3.93
3.92
3.91
3.90
3.52
3.51
3.50
3.49
3.47
3.46
3.45
2.28
2.20
2.17
2.14
1.63
1.56
1.31
1.23
1.06
1.04
1.02
1.00
0.89
0.87
0.86
Me
Me
O
N
H
NO2
Me
2.108
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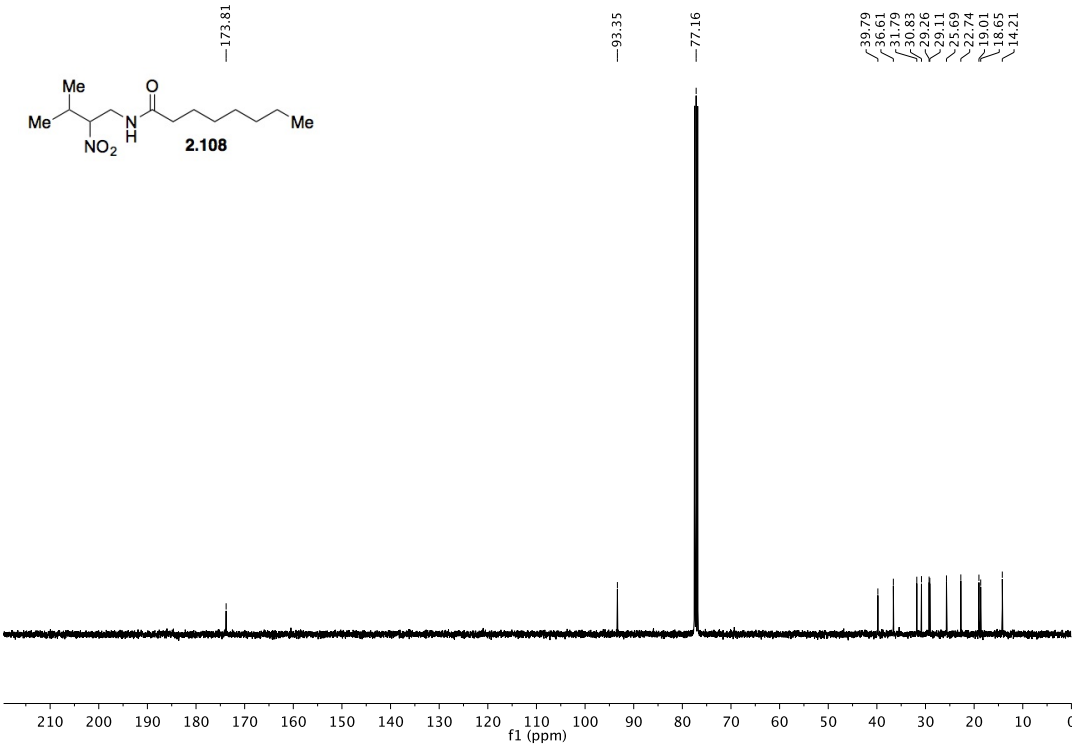
1.00
1.02
1.99
2.15
8.36
2.97
2.96
3.14
f1 (ppm)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93.35
77.16
39.79
36.61
31.79
30.83
29.26
29.11
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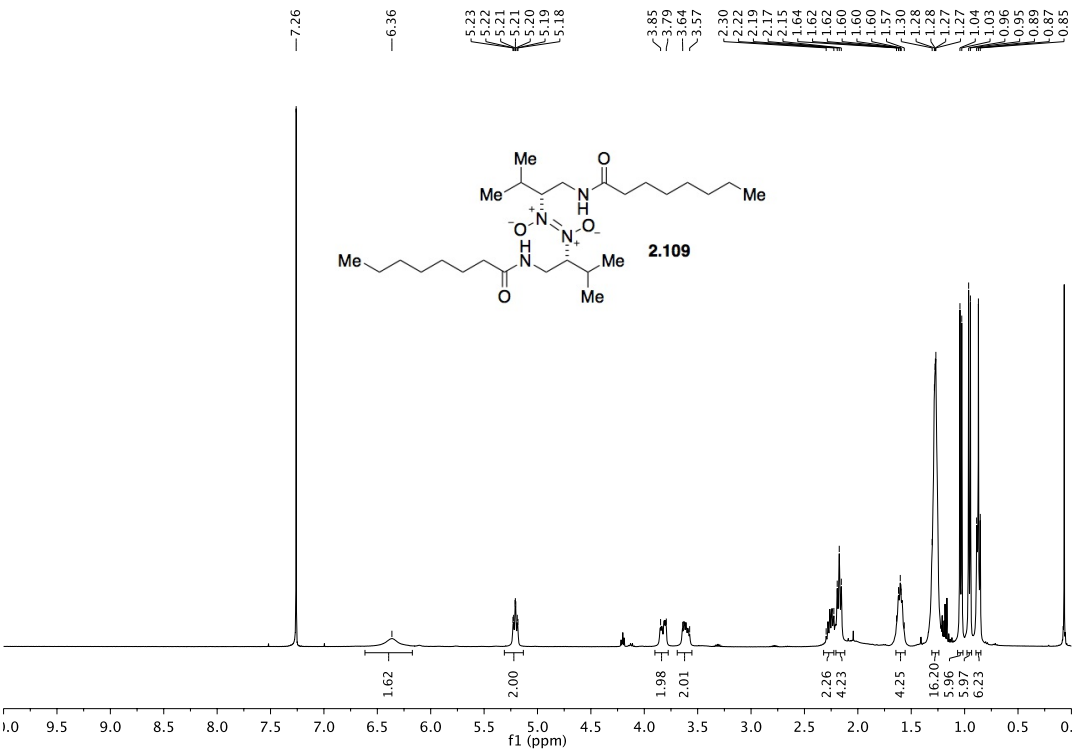
22.74
19.01
18.65
14.21
Me
Me
O
N
H
NO2
Me
2.108
f1 (ppm)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5.23
5.22
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5.19
5.18
3.85
3.79
3.64
3.57
2.30
2.22
2.19
2.17
2.15
1.64
1.62
1.62
1.60
1.60
1.60
1.57
1.30
1.28
1.28
1.27
1.27
1.04
1.03
0.96
0.95
0.89
0.87
0.85
Me
O
Me
N
H
N
O
N
O
Me
H
N
Me
O
Me
2.109
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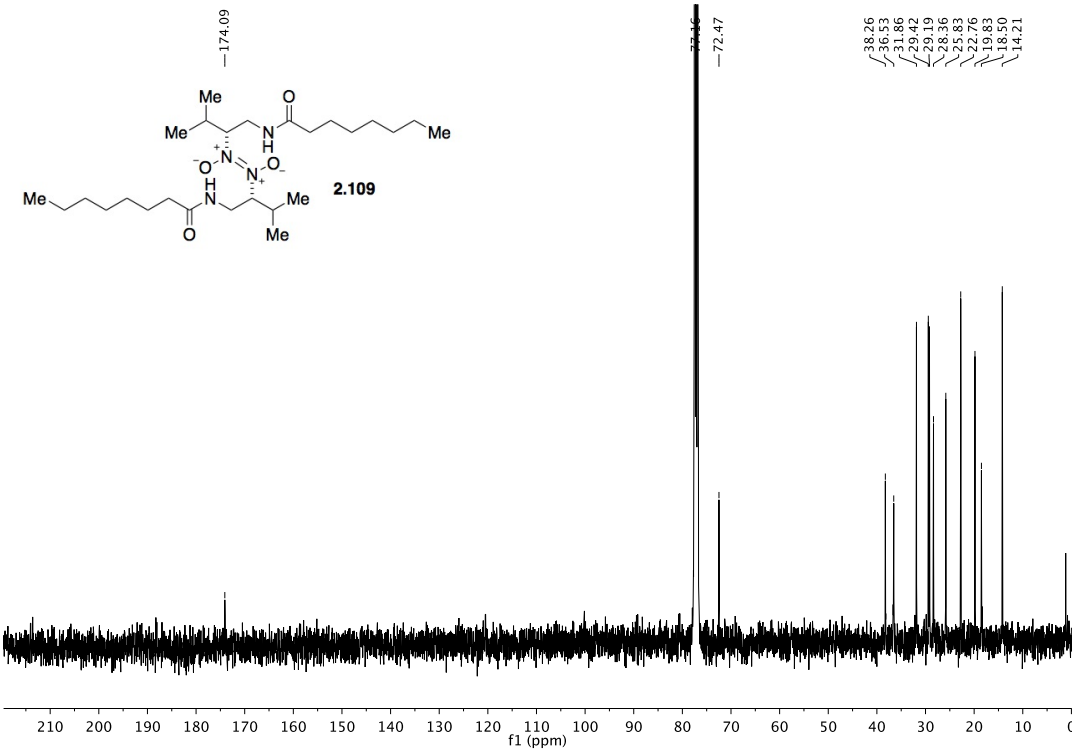
2.01
2.26
4.23
4.25
16.20
5.96
5.97
6.23
f1 (ppm)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72.47
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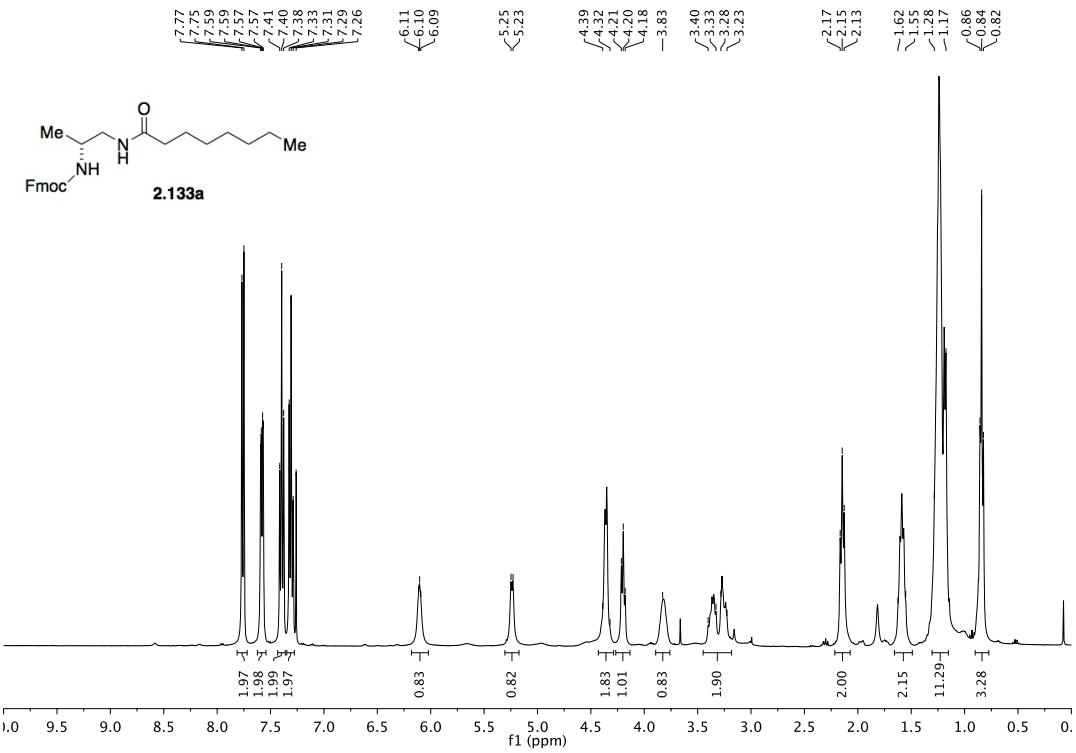
31.86
29.42
29.19
28.36
25.83
22.76
19.83
18.50
14.21
Me
O
Me
N
H
N
O
N
O
Me
H
N
Me
O
Me
2.109
f1 (ppm)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7.33
7.31
7.29
7.26
6.11
6.10
6.09
5.25
5.23
4.39
4.32
4.21
4.20
4.18
3.83
3.40
3.33
3.28
3.23
2.17
2.15
2.13
1.62
1.55
1.28
1.17
0.86
0.84
0.82
Me
O
N
H
Me
NH
Fmoc
2.133a
1.97
1.98
1.99
1.97
0.83
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1.83
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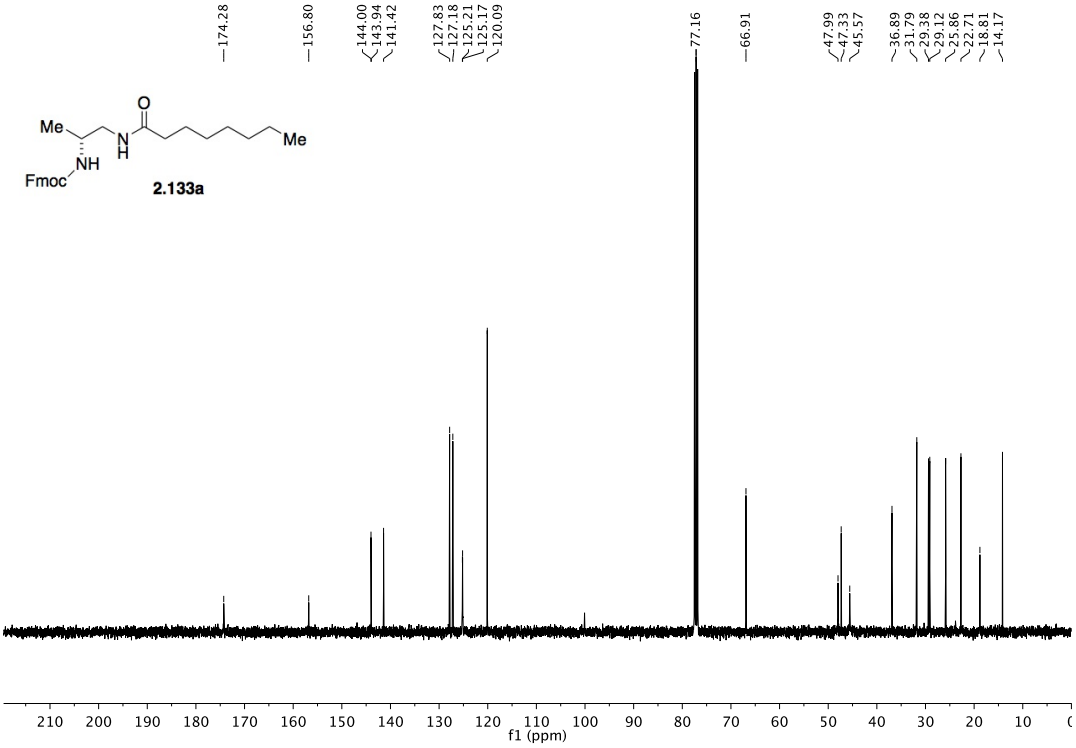
0.83
1.90
2.00
2.15
11.29
3.28
f1 (ppm)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125.17
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77.16
66.91
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47.33
45.57
36.89
31.79
29.38
29.12
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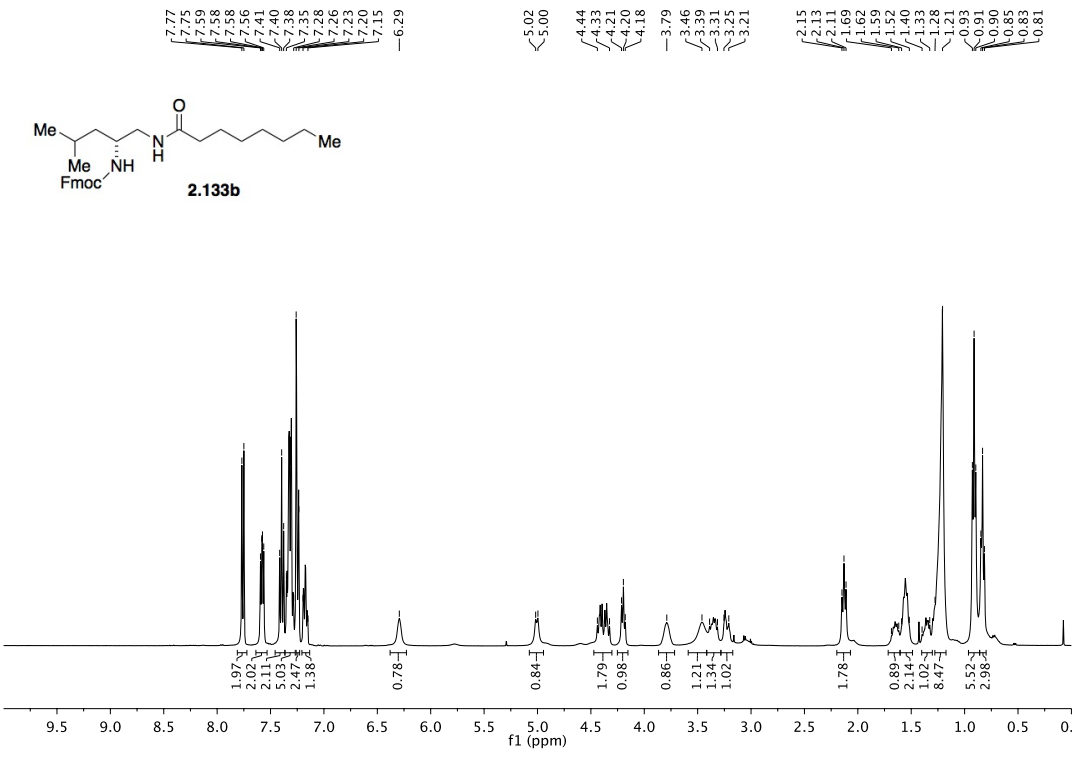
22.71
18.81
14.17
Me
O
N
H
Me
NH
Fmoc
2.133a
f1 (ppm)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7.28
7.26
7.23
7.20
7.15
6.29
5.02
5.00
4.44
4.33
4.21
4.20
4.18
3.79
3.46
3.39
3.31
3.25
3.21
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2.13
2.11
1.69
1.62
1.59
1.52
1.40
1.33
1.28
1.21
0.93
0.91
0.90
0.85
0.83
0.81
Me
Me
NH
Fmoc
N
H
O
Me
2.133b
1.97
2.02
2.11
5.03
2.47
1.38
0.78
0.84
1.79
0.98
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1.21
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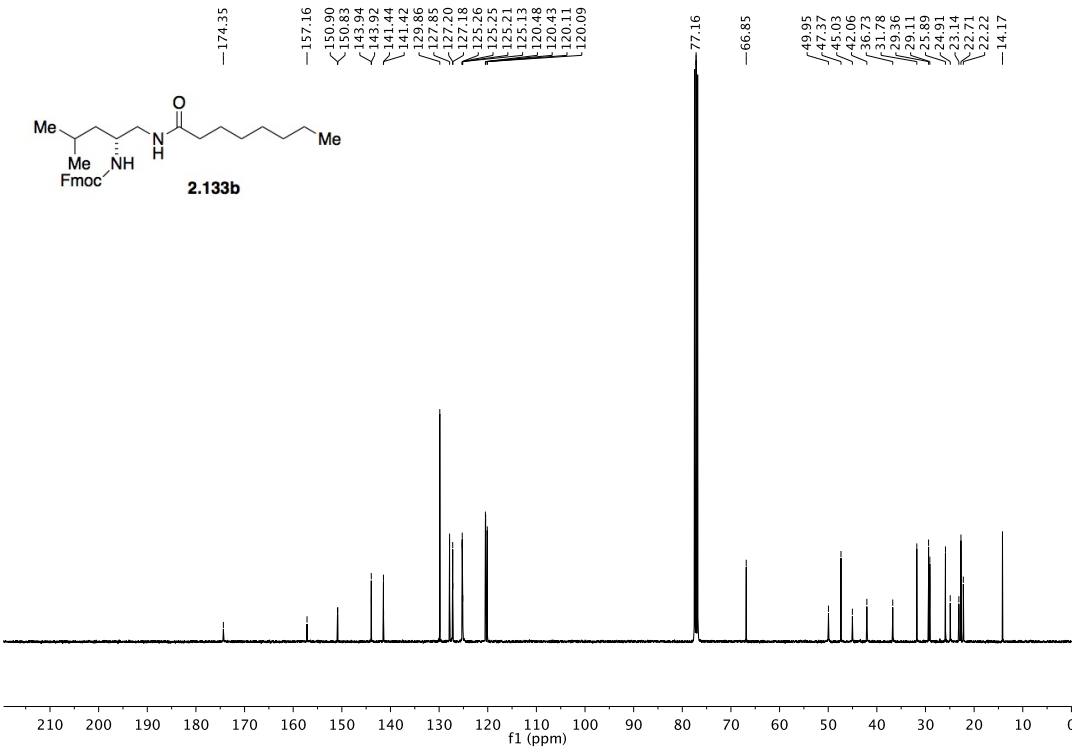
1.02
1.78
0.89
2.14
1.02
8.47
5.52
2.98
f1 (ppm)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127.20
127.18
125.26
125.25
125.21
125.13
120.48
120.43
120.11
120.09
77.16
66.85
49.95
47.37
45.03
42.06
36.73
31.78
29.36
29.11
25.89
24.91
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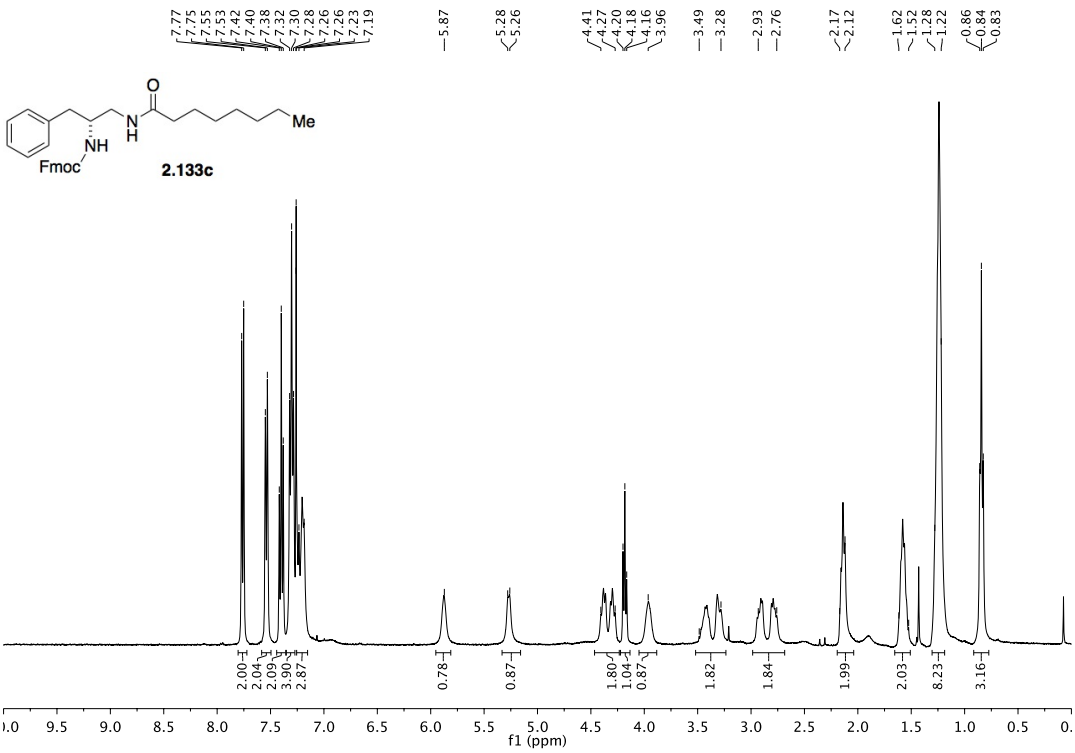
22.22
14.17
Me
Me
NH
Fmoc
N
H
O
Me
2.133b
f1 (ppm)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7.23
7.19
5.87
5.28
5.26
4.41
4.27
4.20
4.18
4.16
3.96
3.49
3.28
2.93
2.76
2.17
2.12
1.62
1.52
1.28
1.22
0.86
0.84
0.83
O
N
H
Me
NH
Fmoc
2.133c
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2.04
2.09
3.90
2.87
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1.04
0.87
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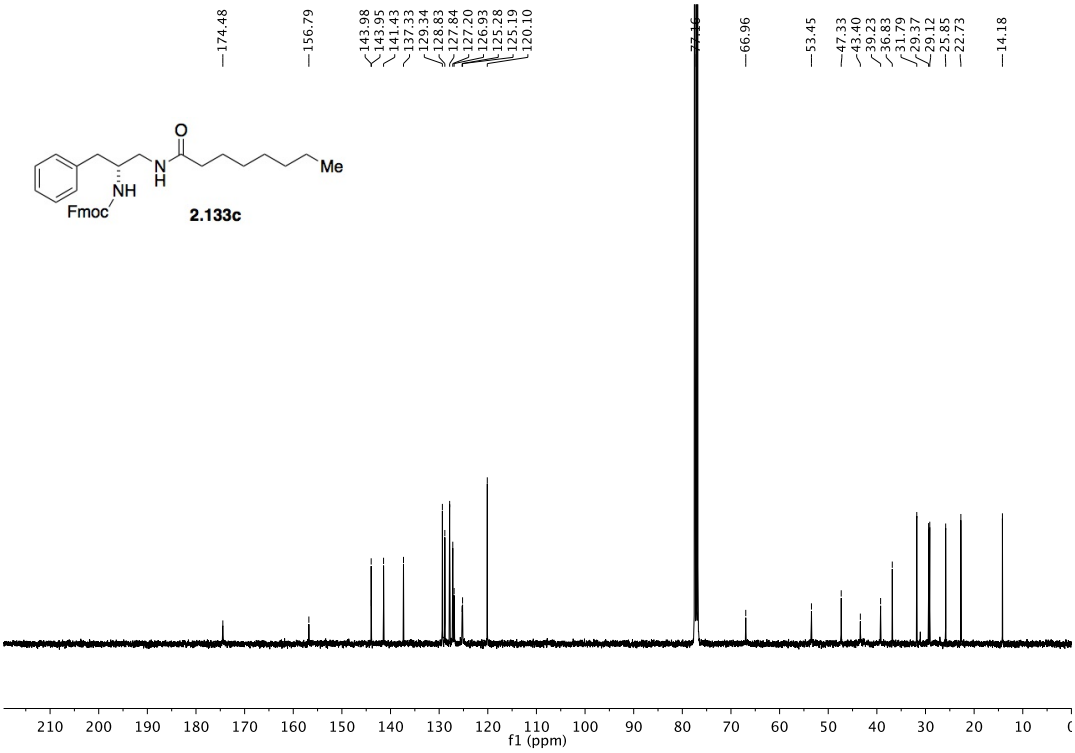
1.84
1.99
2.03
8.23
3.16
f1 (ppm)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125.28
125.19
120.10
77.16
66.96
53.45
47.33
43.40
39.23
36.83
31.79
29.37
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25.85
22.73
14.18
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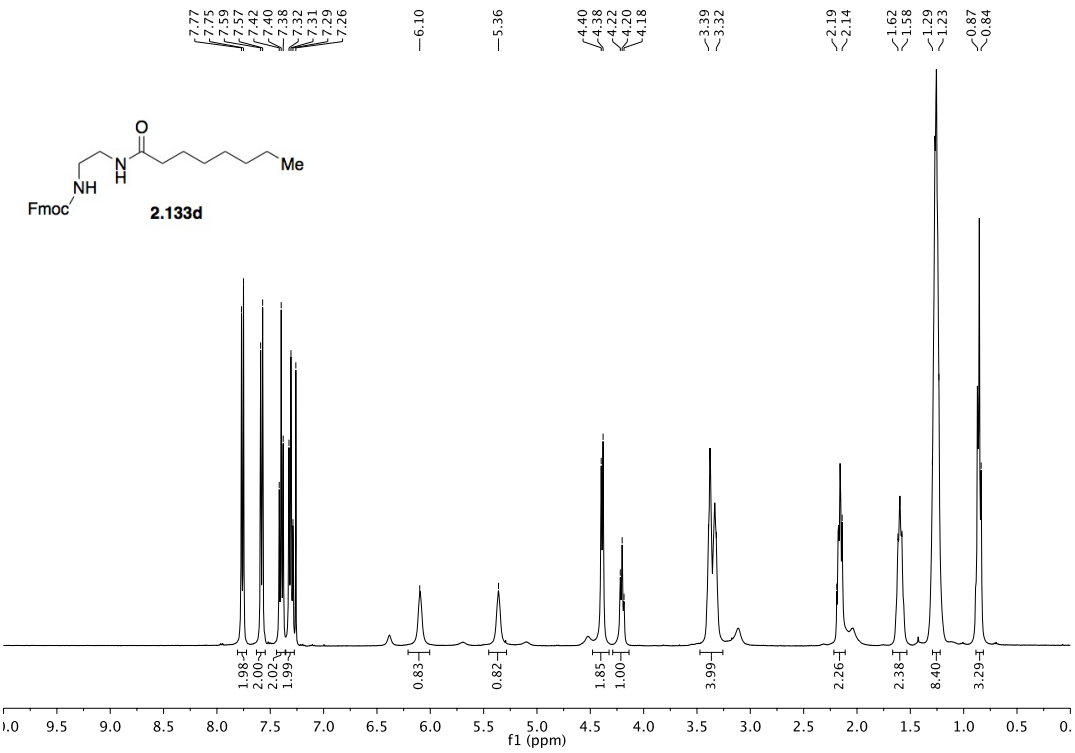
N
H
Me
NH
Fmoc
2.133c
f1 (ppm)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7.32
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4.40
4.38
4.22
4.20
4.18
3.39
3.32
2.19
2.14
1.62
1.58
1.29
1.23
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0.84
O
N
H
NH
Fmoc
Me
2.133d
1.98
2.00
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1.85
1.00
3.99
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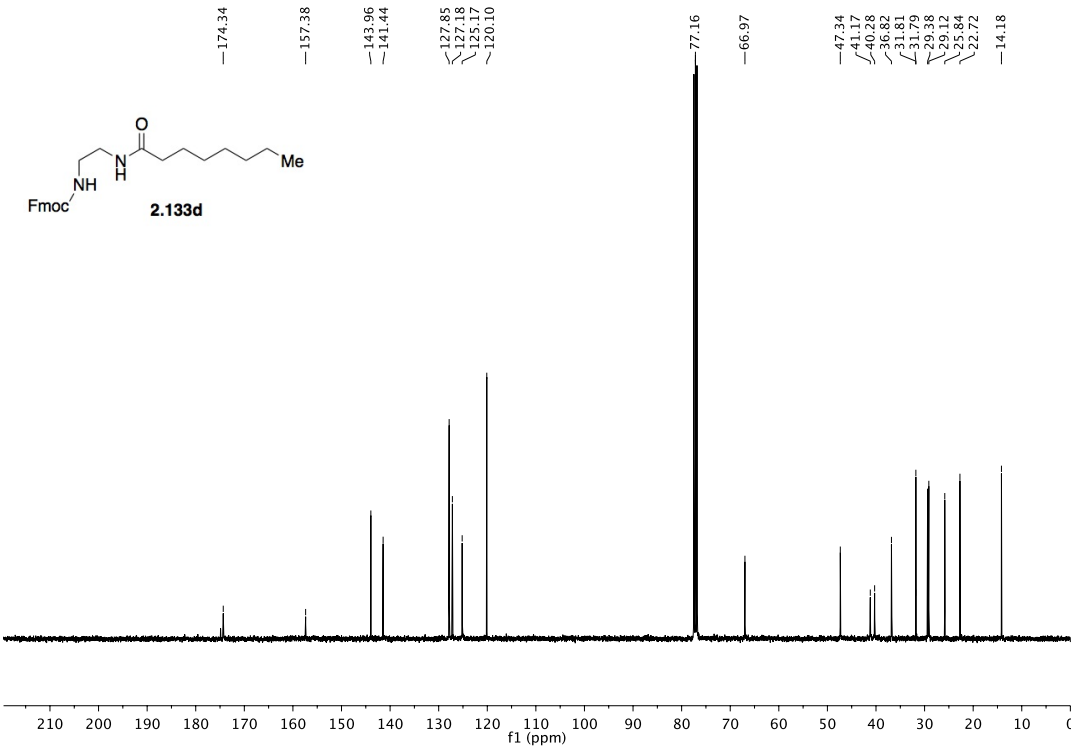
2.38
8.40
3.29
f1 (ppm)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127.18
125.17
120.10
77.16
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41.17
40.28
36.82
31.81
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29.38
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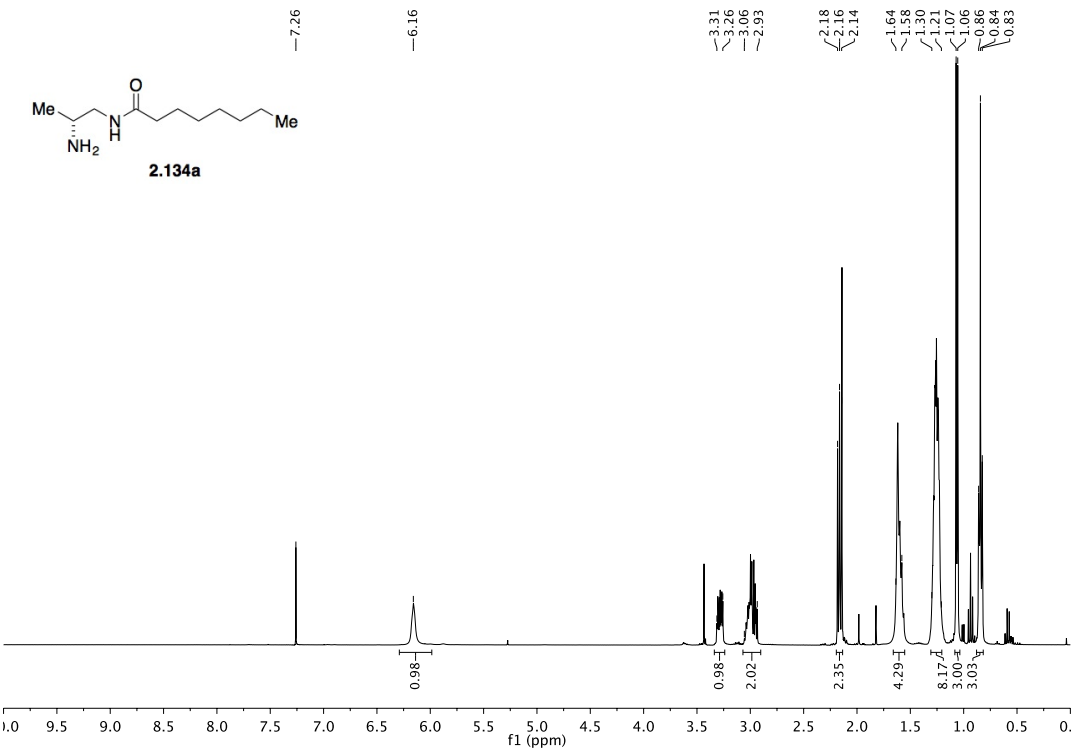
25.84
22.72
14.18
O
N
H
NH
Fmoc
Me
2.133d
f1 (ppm)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3.31
3.26
3.06
2.93
2.18
2.16
2.14
1.64
1.58
1.30
1.21
1.07
1.06
0.86
0.84
0.83
Me
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H
NH2
O
Me
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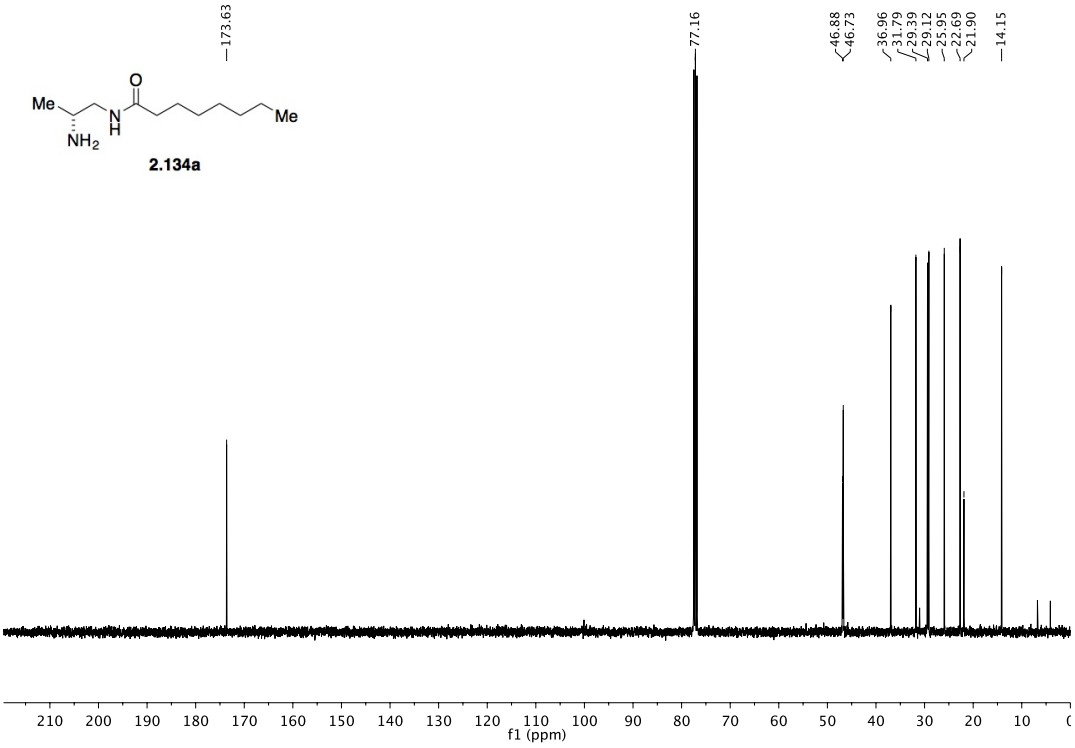
0.98
0.98
2.02
2.35
4.29
8.17
3.00
3.03
f1 (ppm)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46.73
36.96
31.79
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29.12
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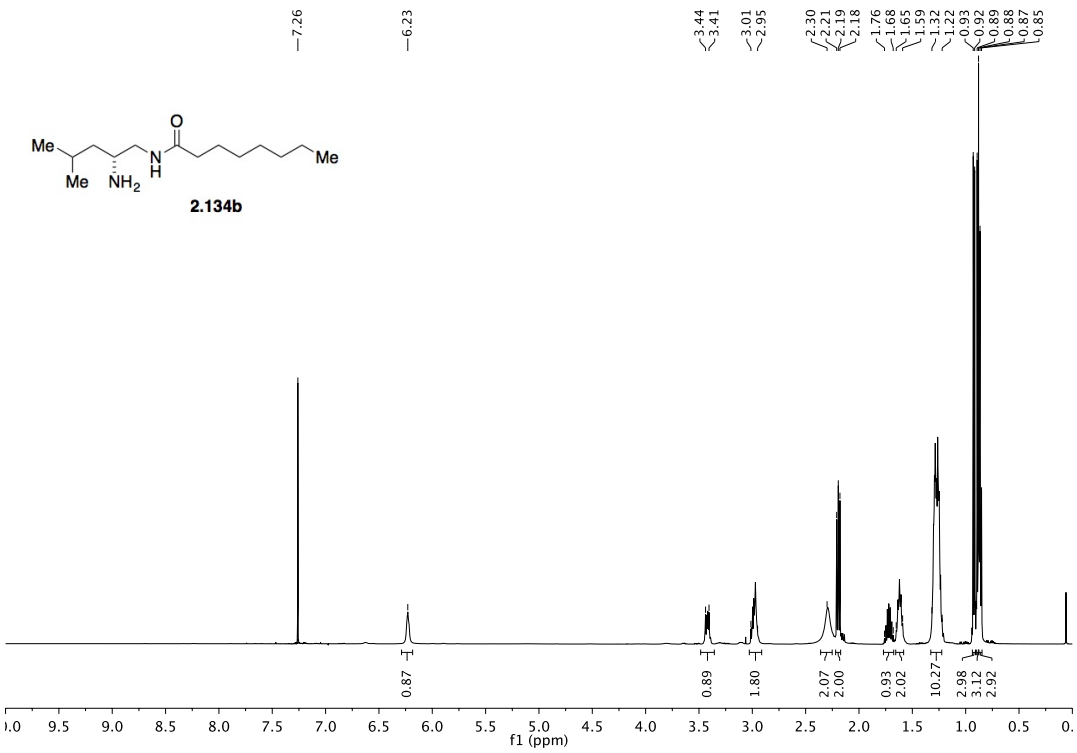
22.69
21.90
14.15
Me
N
H
NH2
O
Me
2.134a
f1 (ppm)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2.95
2.30
2.21
2.19
2.18
1.76
1.68
1.65
1.59
1.32
1.22
0.93
0.92
0.89
0.88
0.87
0.85
Me
Me
NH2
N
H
O
Me
2.134b
0.87
0.89
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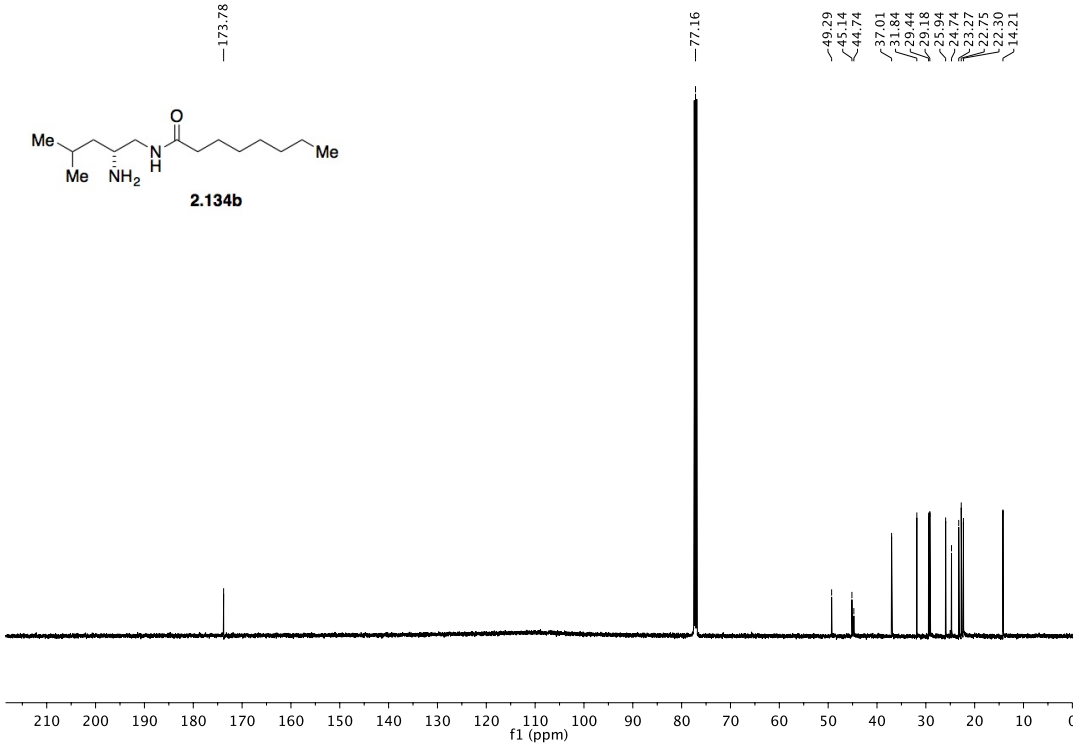
2.07
2.00
0.93
2.02
10.27
2.98
3.12
2.92
f1 (ppm)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37.01
31.84
29.44
29.18
25.94
24.74
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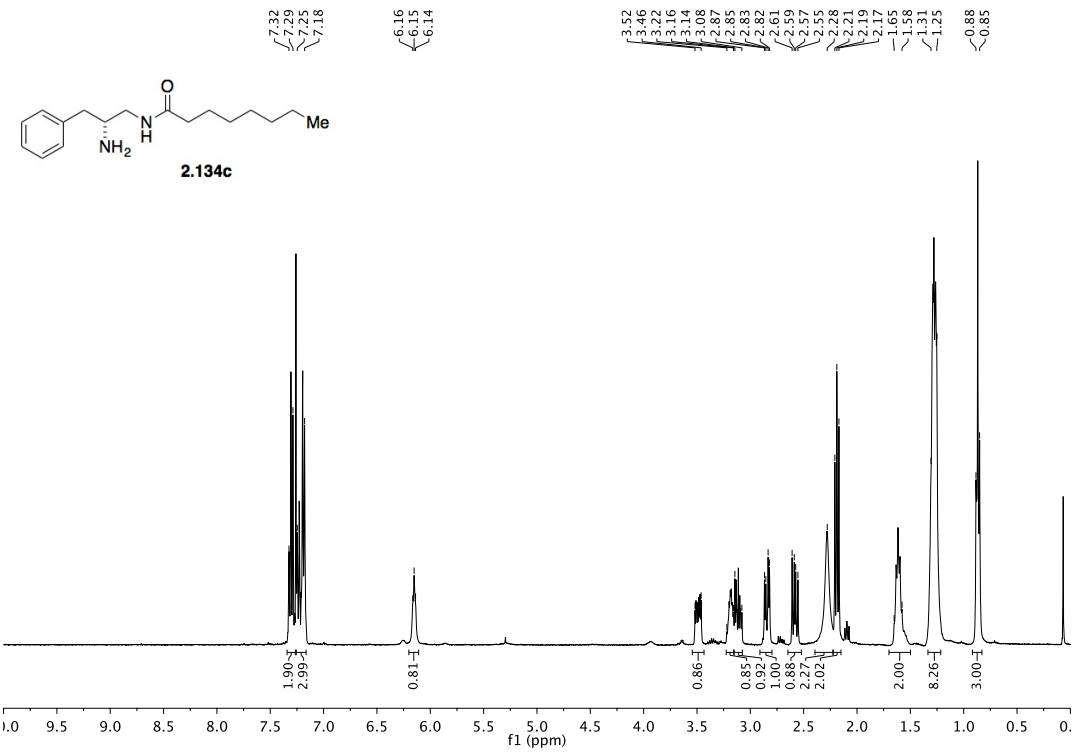
22.75
22.30
14.21
Me
Me
NH2
N
H
O
Me
2.134b
f1 (ppm)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6.15
6.14
3.52
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3.22
3.16
3.14
3.08
2.87
2.85
2.83
2.82
2.61
2.59
2.57
2.55
2.28
2.21
2.19
2.17
1.65
1.58
1.31
1.25
0.88
0.85
O
N
H
NH2
Me
2.134c
1.90
2.99
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0.92
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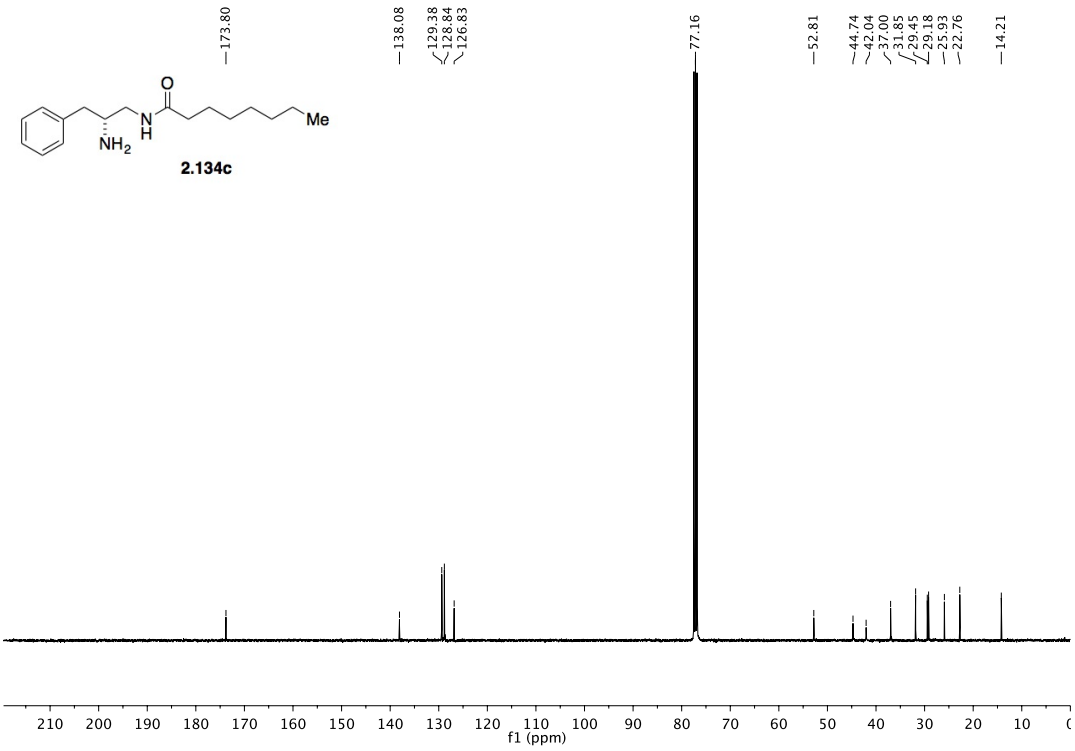
0.88
2.27
2.02
2.00
8.26
3.00
f1 (ppm)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44.74
42.04
37.00
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29.18
25.93
22.76
14.21
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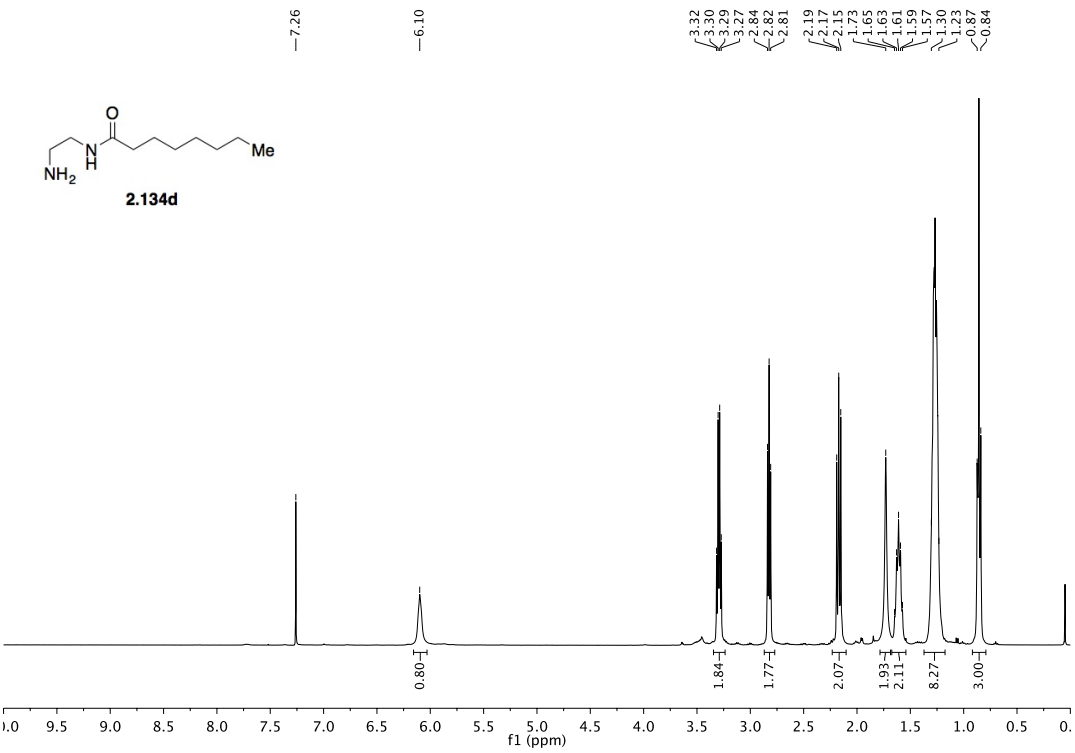
N
H
NH2
Me
2.134c
f1 (ppm)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3.27
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2.82
2.81
2.19
2.17
2.15
1.73
1.65
1.63
1.61
1.59
1.57
1.30
1.23
0.87
0.84
O
N
H
NH2
Me
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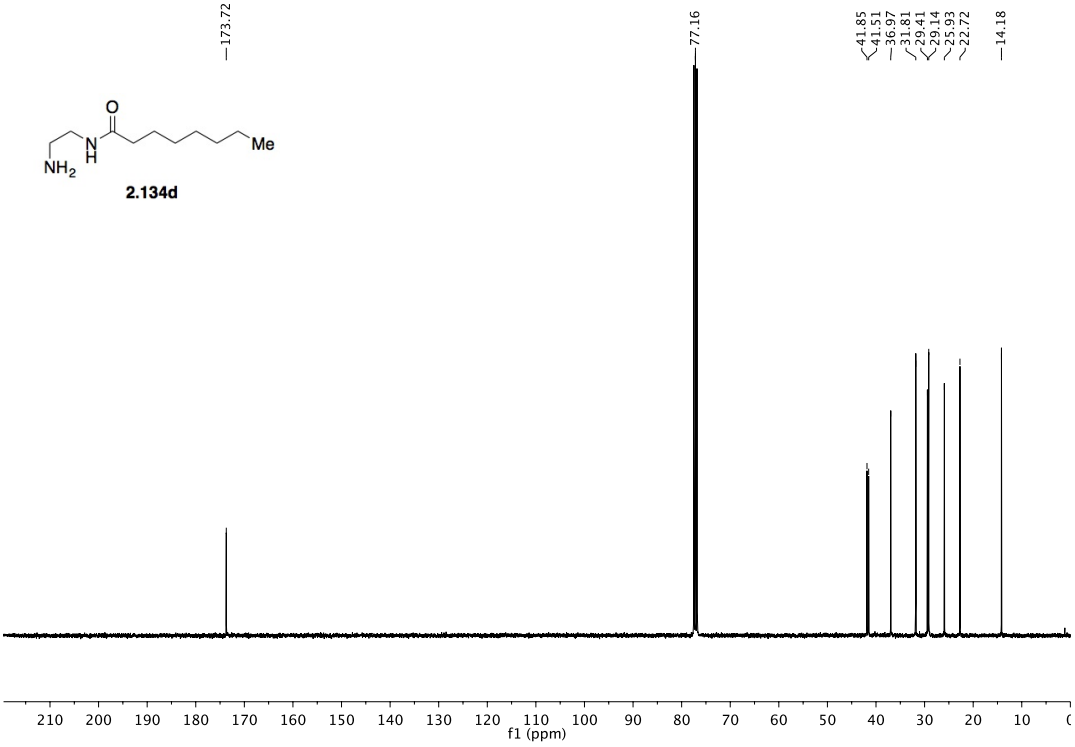
0.80
1.84
1.77
2.07
1.93
2.11
8.27
3.00
f1 (ppm)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29.14
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22.72
14.18
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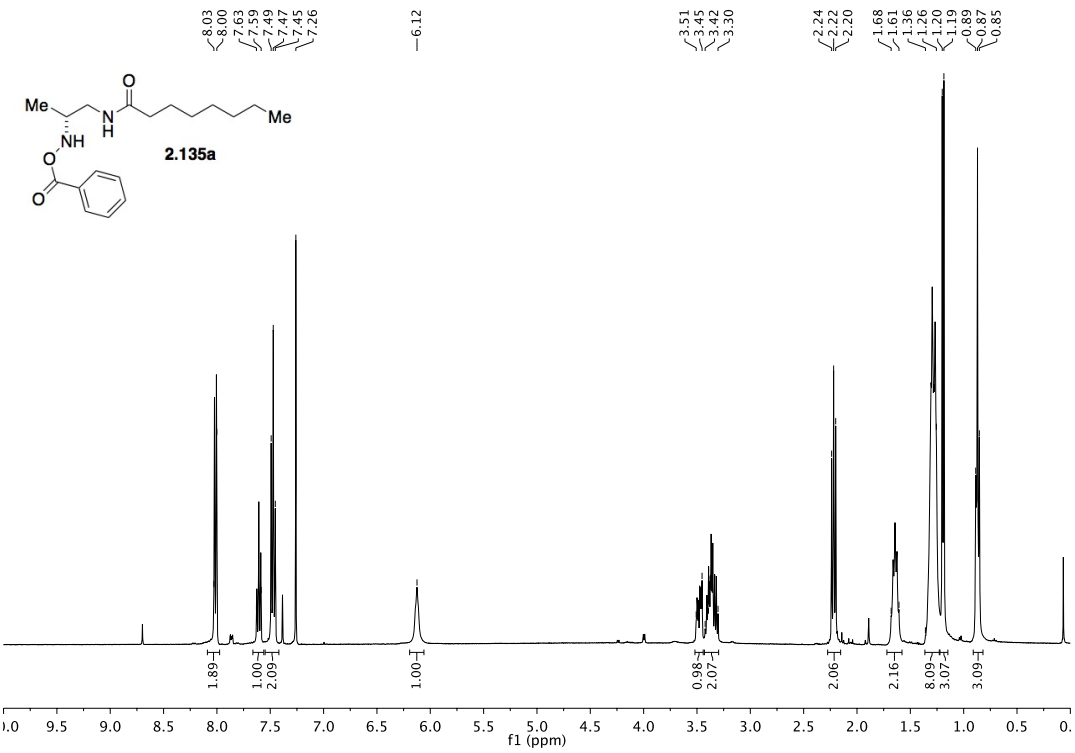
N
H
NH2
Me
2.134d
f1 (ppm)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8.00
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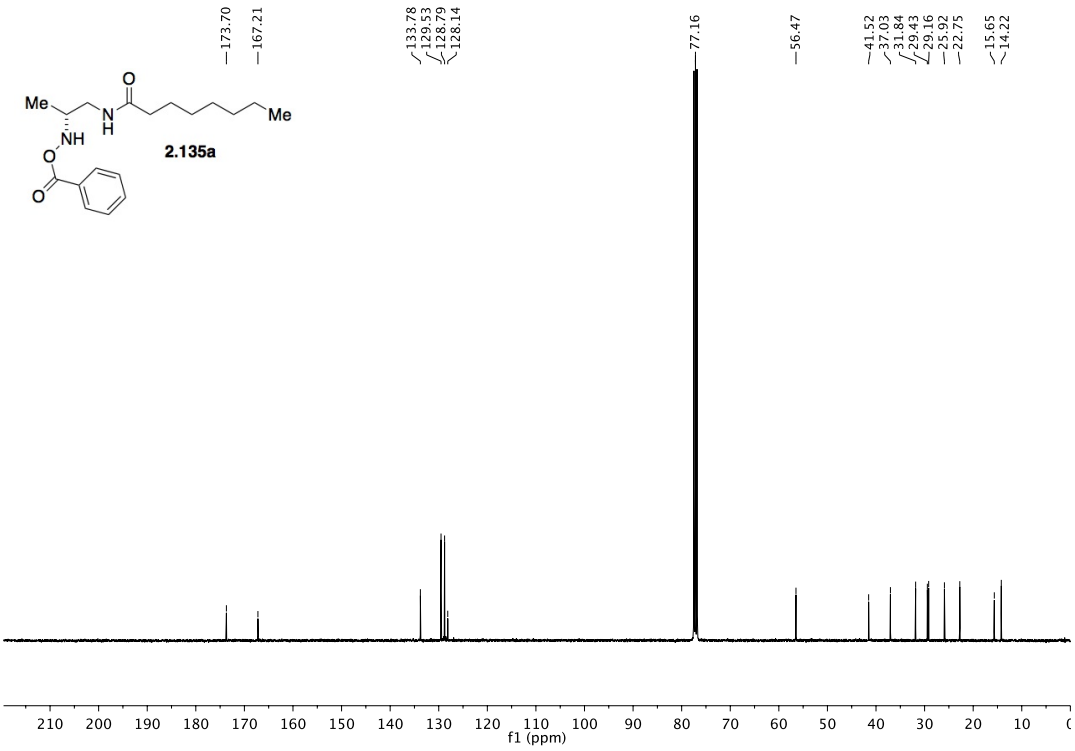
7.47
7.45
7.26
6.12
3.51
3.45
3.42
3.30
2.24
2.22
2.20
1.68
1.61
1.36
1.26
1.20
1.19
0.89
0.87
0.85
Me
N
H
O
NH
O
O
Me
2.135a
1.89
1.00
2.09
1.00
0.98
2.07
2.06
2.16
8.09
3.07
3.09
f1 (ppm)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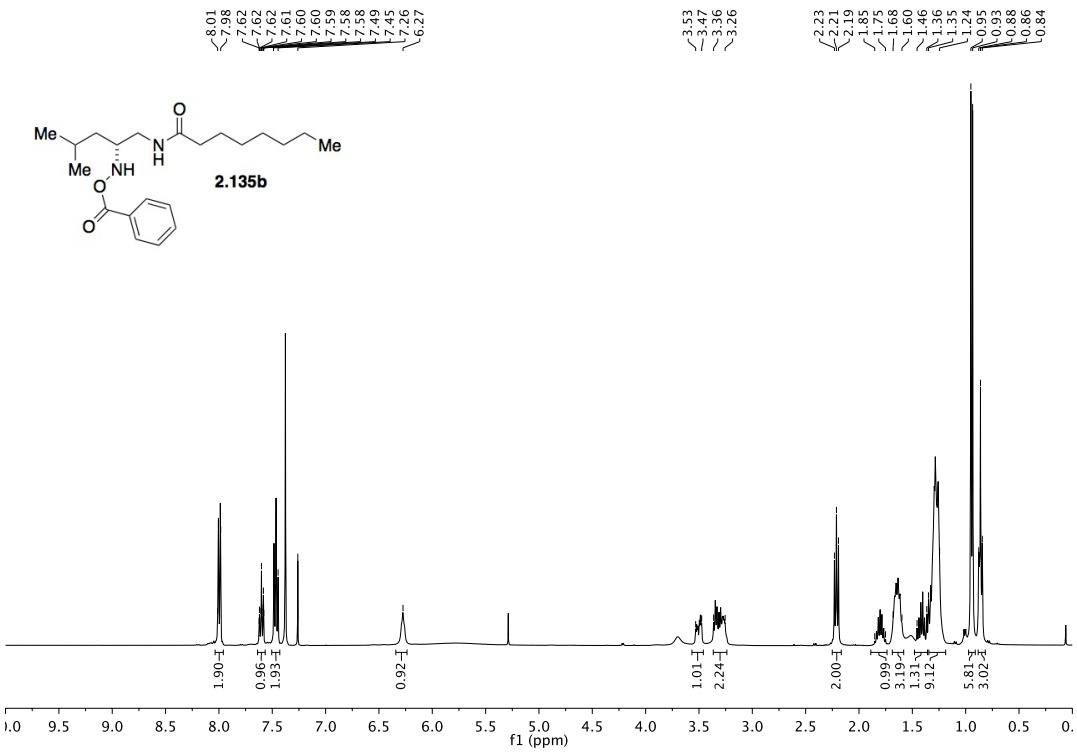
133.78
129.53
128.79
128.14
77.16
56.47
41.52
37.03
31.84
29.43
29.16
25.92
22.75
15.65
14.22
Me
N
H
O
NH
O
O
Me
2.135a
f1 (ppm)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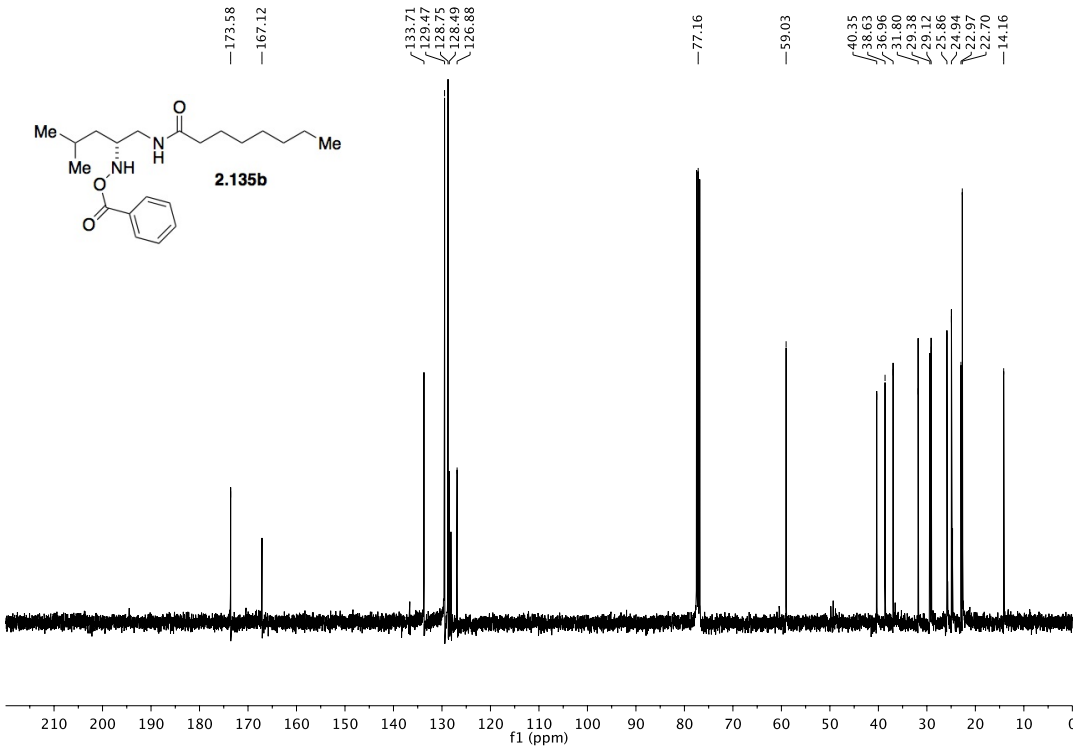
7.98
7.62
7.62
7.62
7.61
7.60
7.60
7.59
7.58
7.58
7.49
7.45
7.26
6.27
3.53
3.47
3.36
3.26
2.23
2.21
2.19
1.85
1.75
1.68
1.60
1.46
1.36
1.35
1.24
0.95
0.93
0.88
0.86
0.84
Me
Me
NH
O
N
H
O
Me
O
2.135b
1.90
0.96
1.93
0.92
1.01
2.24
2.00
0.99
3.19
1.31
9.12
5.81
3.02
f1 (ppm)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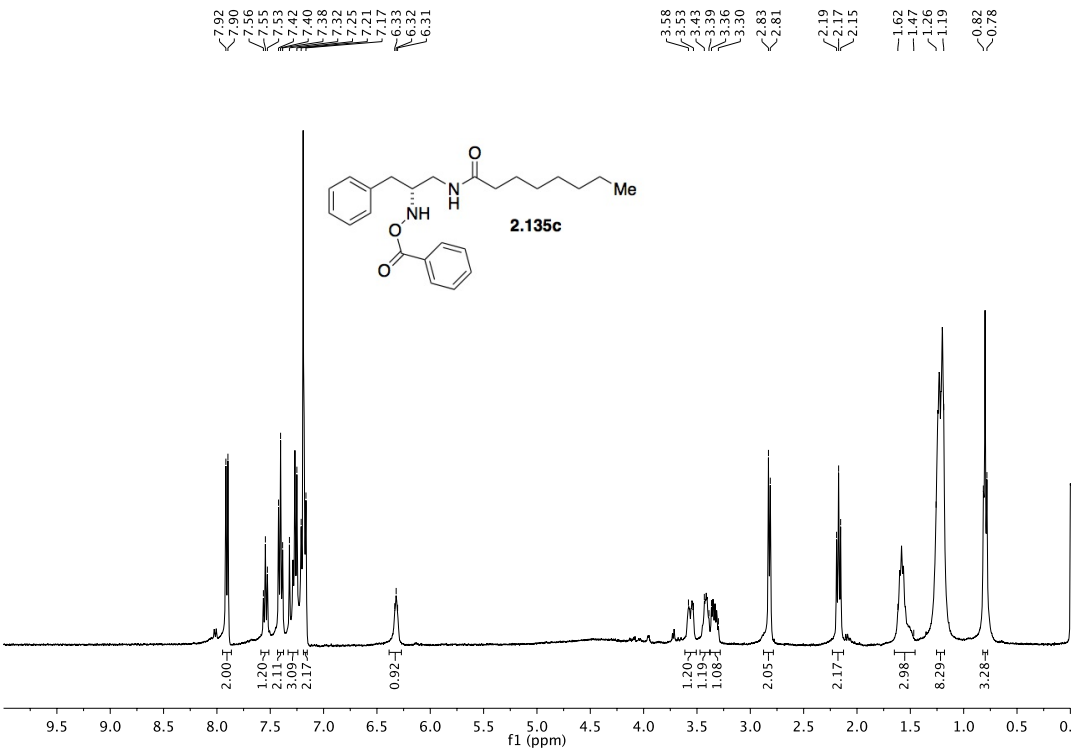
128.49
126.88
77.16
59.03
40.35
38.63
36.96
31.80
29.38
29.12
25.86
24.94
22.97
22.70
14.16
Me
Me
NH
O
N
H
O
Me
O
2.135b
f1 (ppm)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7.90
7.56
7.55
7.53
7.42
7.40
7.38
7.32
7.25
7.21
7.17
6.33
6.32
6.31
3.58
3.53
3.43
3.39
3.36
3.30
2.83
2.81
2.19
2.17
2.15
1.62
1.47
1.26
1.19
0.82
0.78
Me
NH
O
2.135c
2.00
1.20
2.11
3.09
2.17
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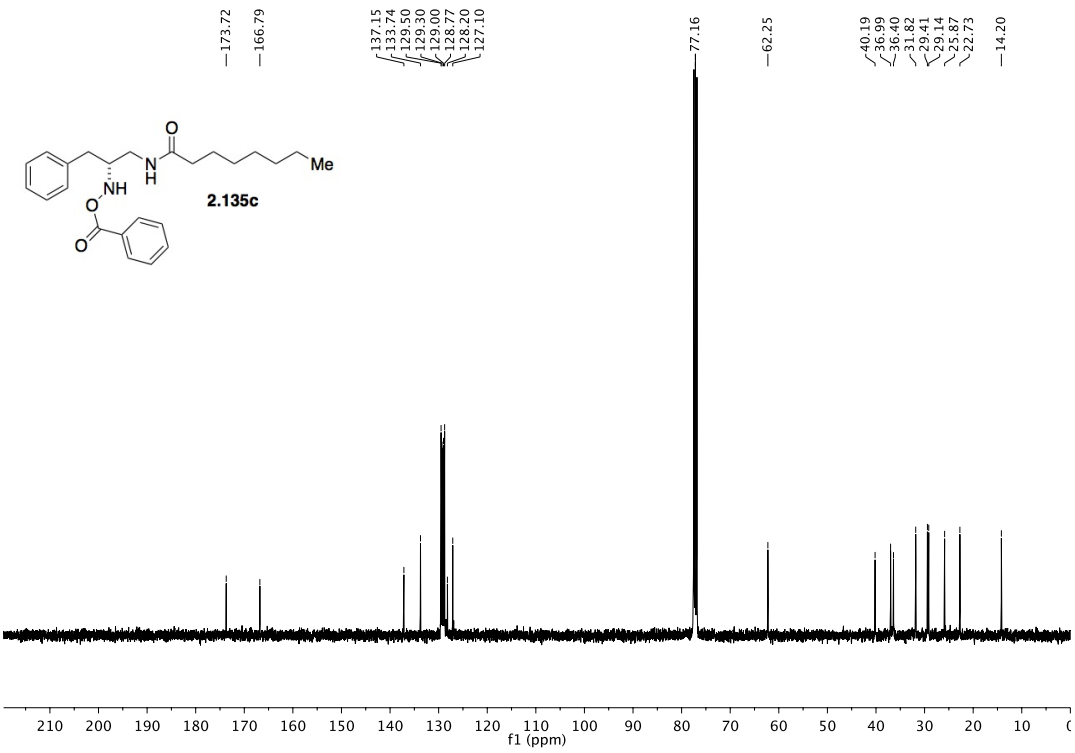
1.20
1.19
1.08
2.05
2.17
2.98
8.29
3.28
f1 (ppm)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137.15
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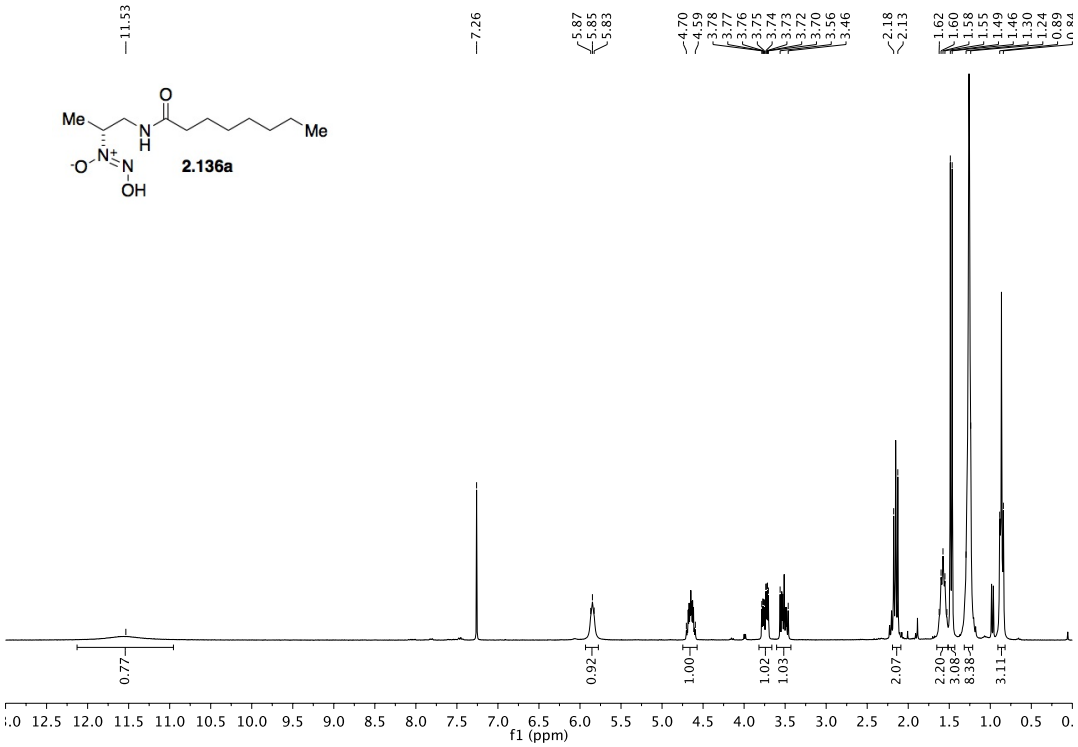
129.50
129.30
129.00
128.77
128.20
127.10
77.16
62.25
40.19
36.99
36.40
31.82
29.41
29.14
25.87
22.73
14.20
Me
NH
O
2.135c
f1 (ppm)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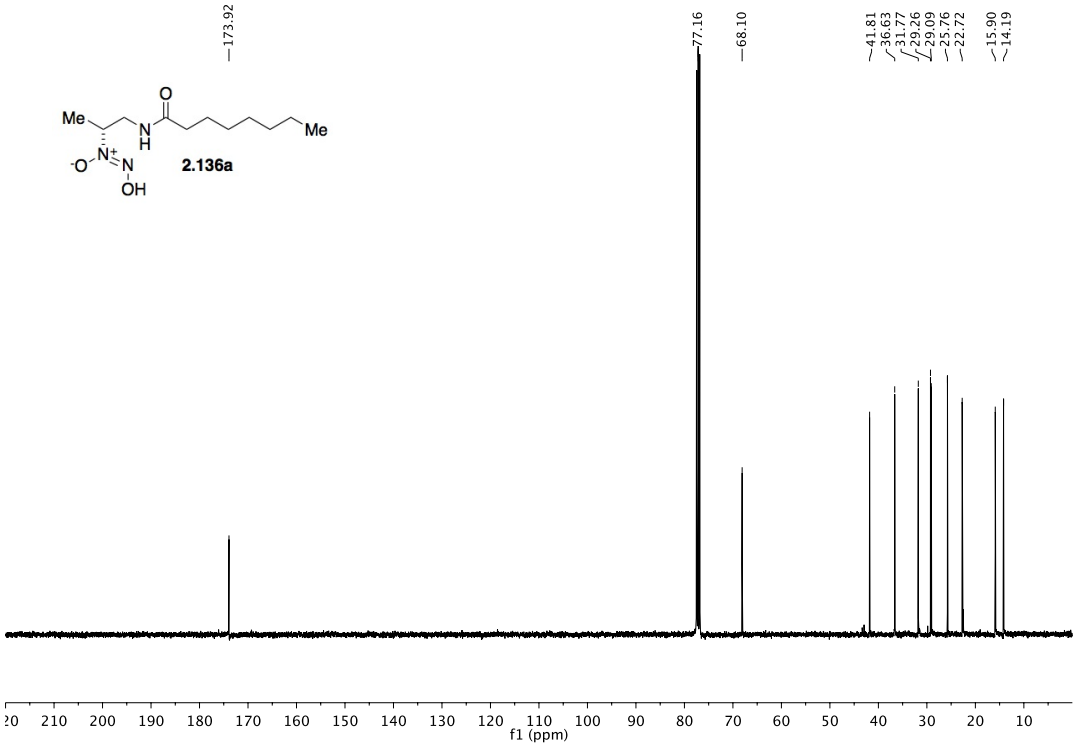
5.87
5.85
5.83
4.70
4.59
3.78
3.77
3.76
3.75
3.74
3.73
3.72
3.70
3.56
3.46
2.18
2.13
1.62
1.60
1.58
1.55
1.49
1.46
1.30
1.24
0.89
Me
Me
2.136a
OH
0.77
0.92
1.00
1.02
1.03
2.07
2.20
3.08
8.38
3.11
f1 (ppm)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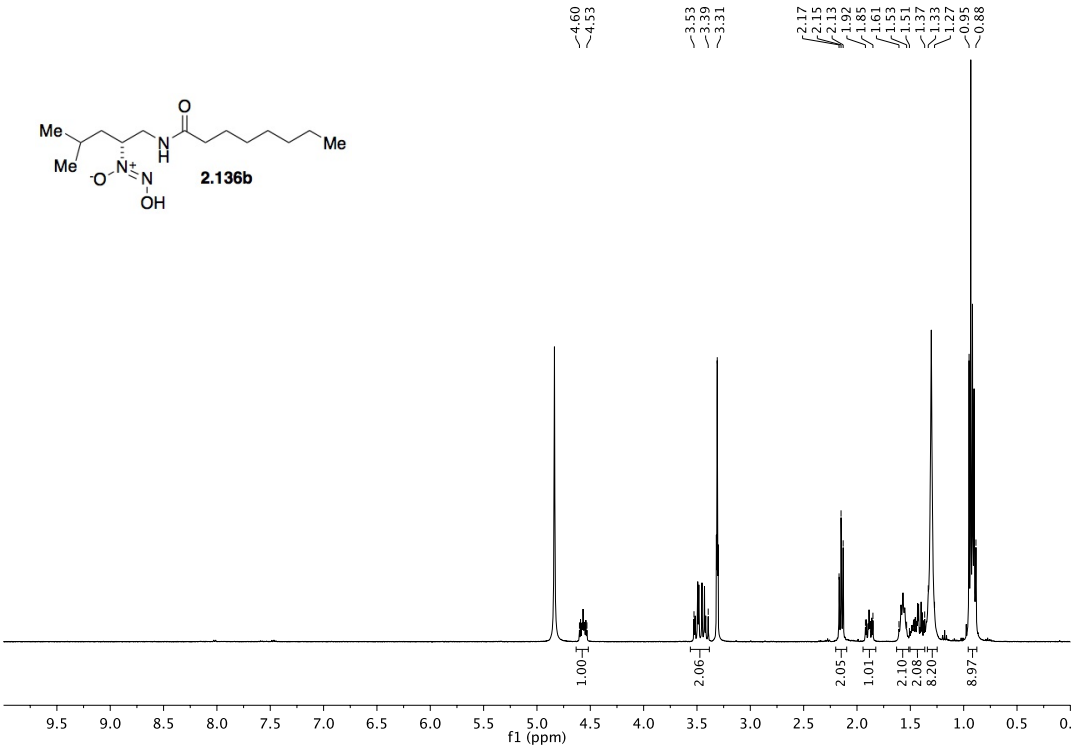
77.16
68.10
41.81
36.63
31.77
29.26
29.09
25.76
22.72
15.90
14.19
Me
Me
2.136a
OH
f1 (ppm)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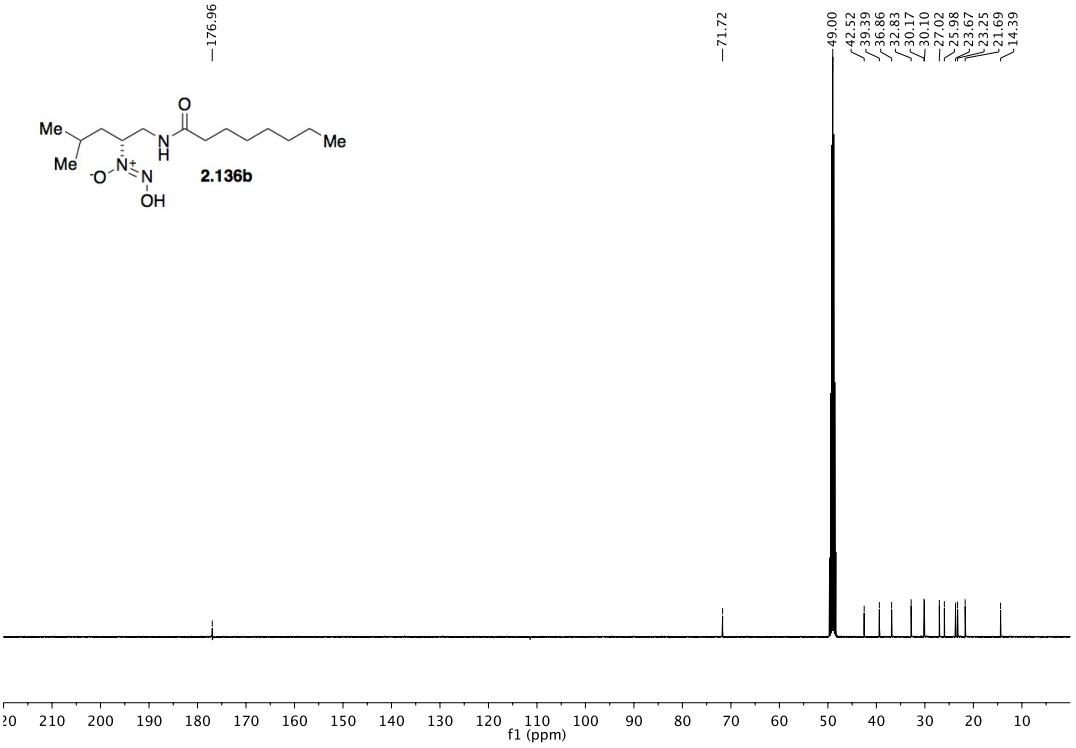
4.53
3.53
3.39
3.31
2.17
2.15
2.13
1.92
1.85
1.61
1.53
1.51
1.37
1.33
1.27
0.95
0.88
Me
Me
O
N
H
Me
N+
O-
N
OH
2.136b
1.00
2.06
2.05
1.01
2.10
2.08
8.20
8.97
f1 (ppm)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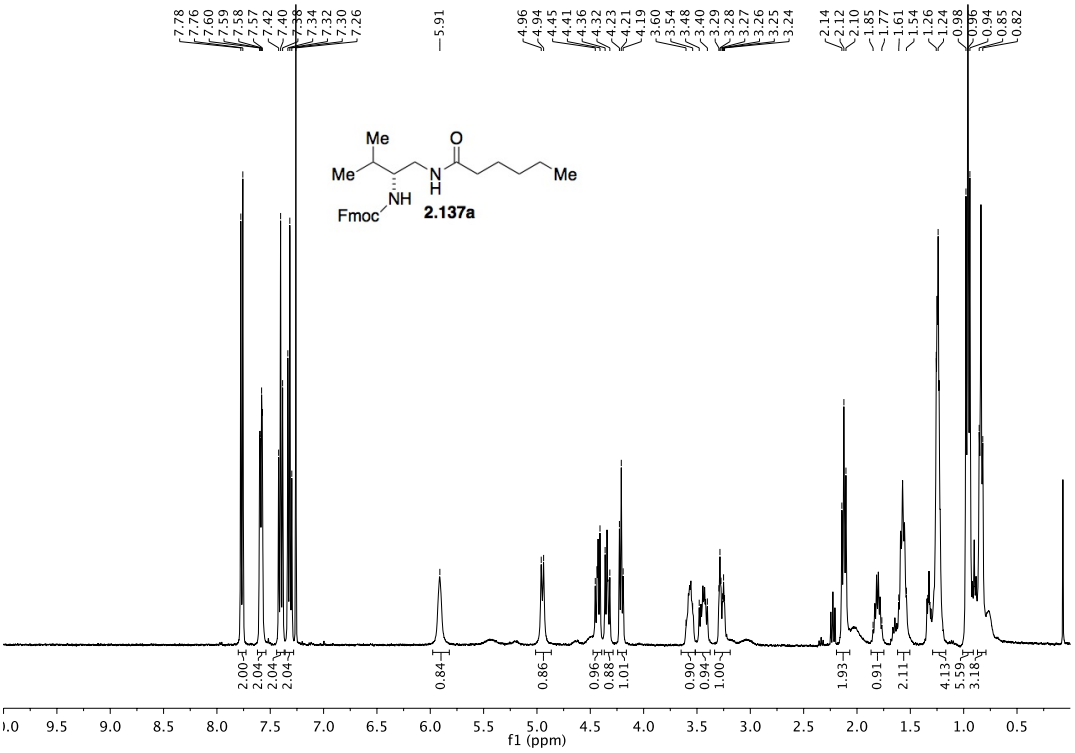
36.86
32.83
30.17
30.10
27.02
25.98
23.67
23.25
21.69
14.39
Me
Me
O
N
H
Me
N+
O-
N
OH
2.136b
f1 (ppm)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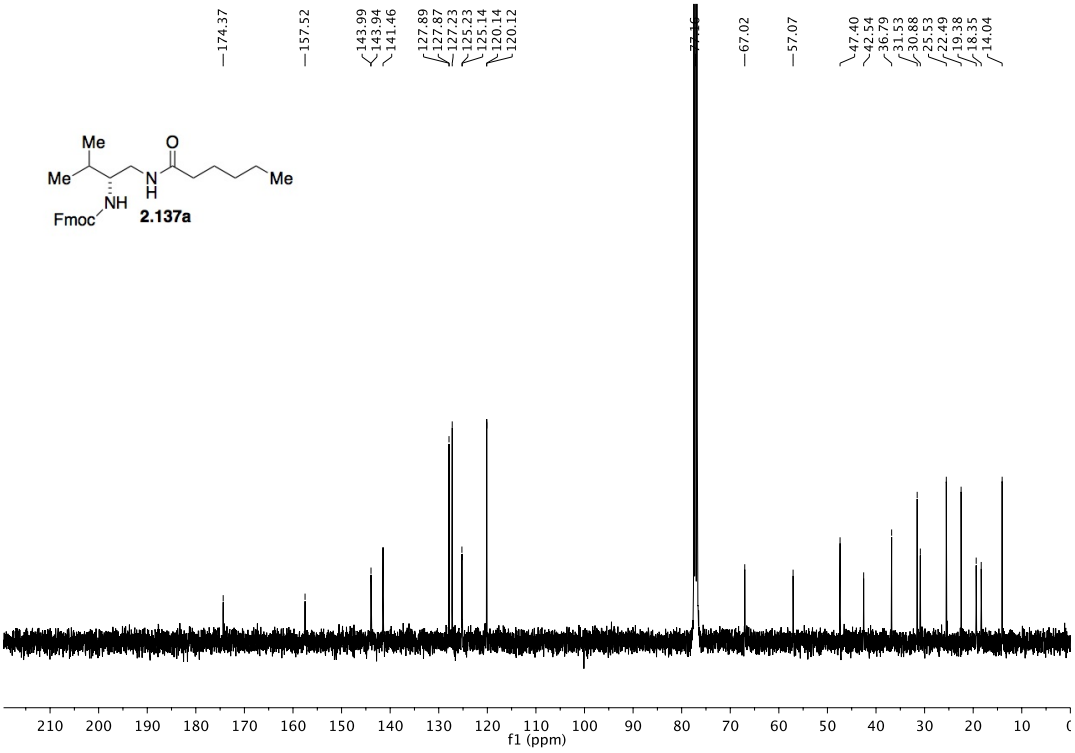
7.42
7.40
7.38
7.34
7.32
7.30
7.26
5.91
4.96
4.94
4.45
4.41
4.36
4.32
4.23
4.21
4.19
3.60
3.54
3.48
3.40
3.29
3.28
3.27
3.26
3.25
3.24
2.14
2.12
2.10
1.85
1.77
1.61
1.54
1.26
1.24
0.98
0.96
0.94
0.85
0.82
Me
Me
O
N
H
NH
Fmoc
Me
2.137a
2.00
2.04
2.04
2.04
0.84
0.86
0.96
0.88
1.01
0.90
0.94
1.00
1.93
0.91
2.11
4.13
5.59
3.18
f1 (ppm)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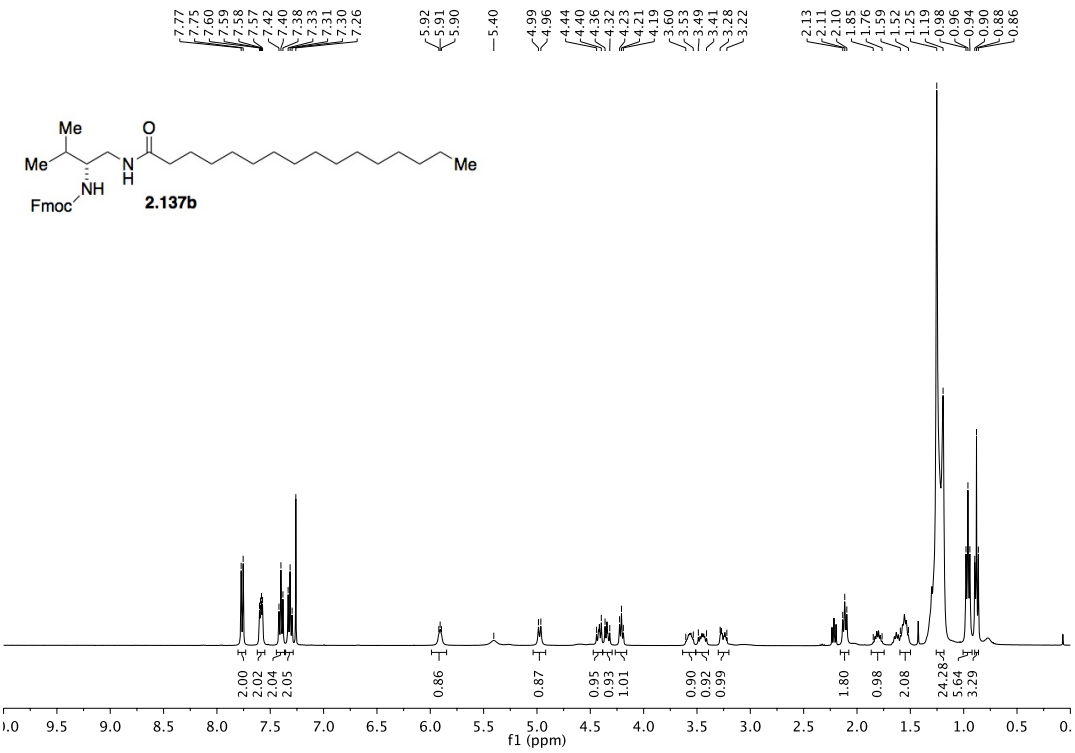
127.87
127.23
125.23
125.14
120.14
120.12
67.02
57.07
47.40
42.54
36.79
31.53
30.88
25.53
22.49
19.38
18.35
14.04
Me
Me
O
N
H
NH
Fmoc
Me
2.137a
f1 (ppm)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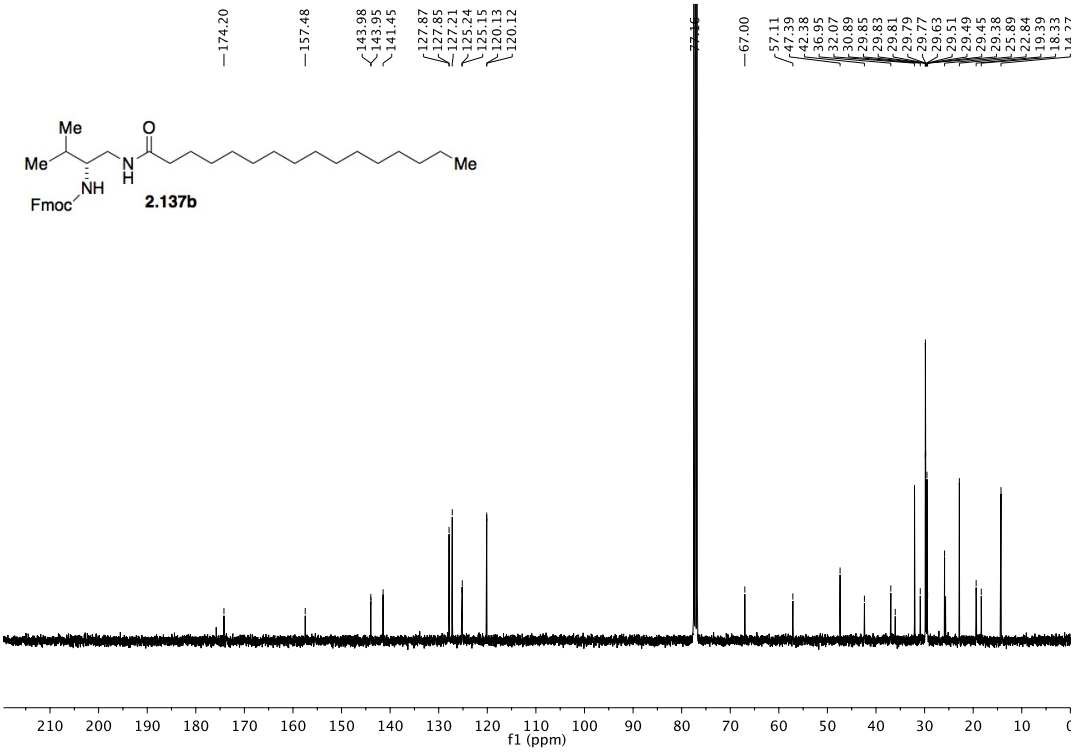
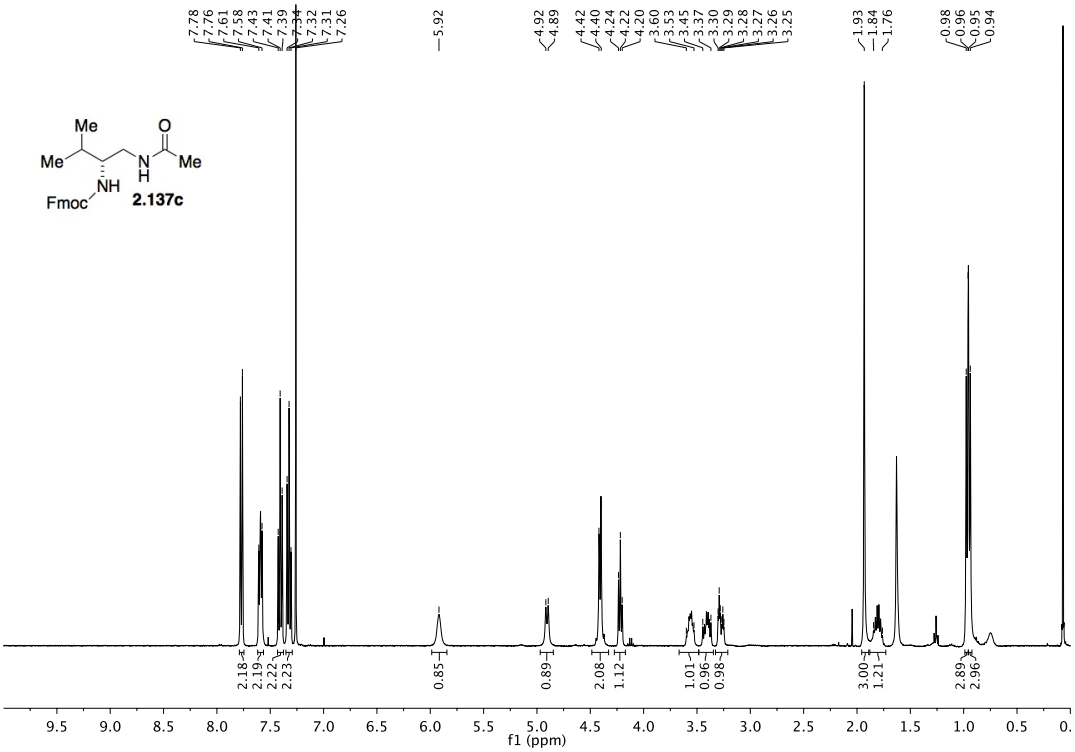
Me
O
N
H
NH
Fmoc
Me
2.137b
f1 (ppm)


Me
Me
O
N
H
NH
Fmoc
Me
2.137b
f1 (ppm)


Me
Me
O
N
H
Me
NH
Fmoc
2.137c
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7.76
7.61
7.58
7.43
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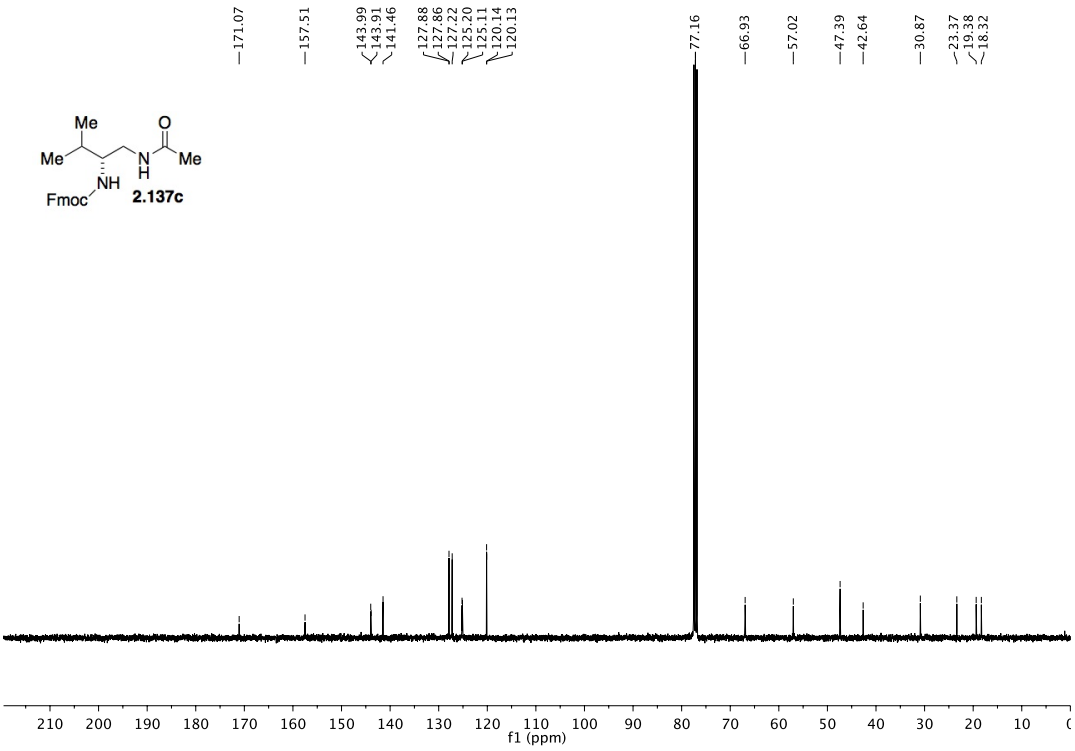
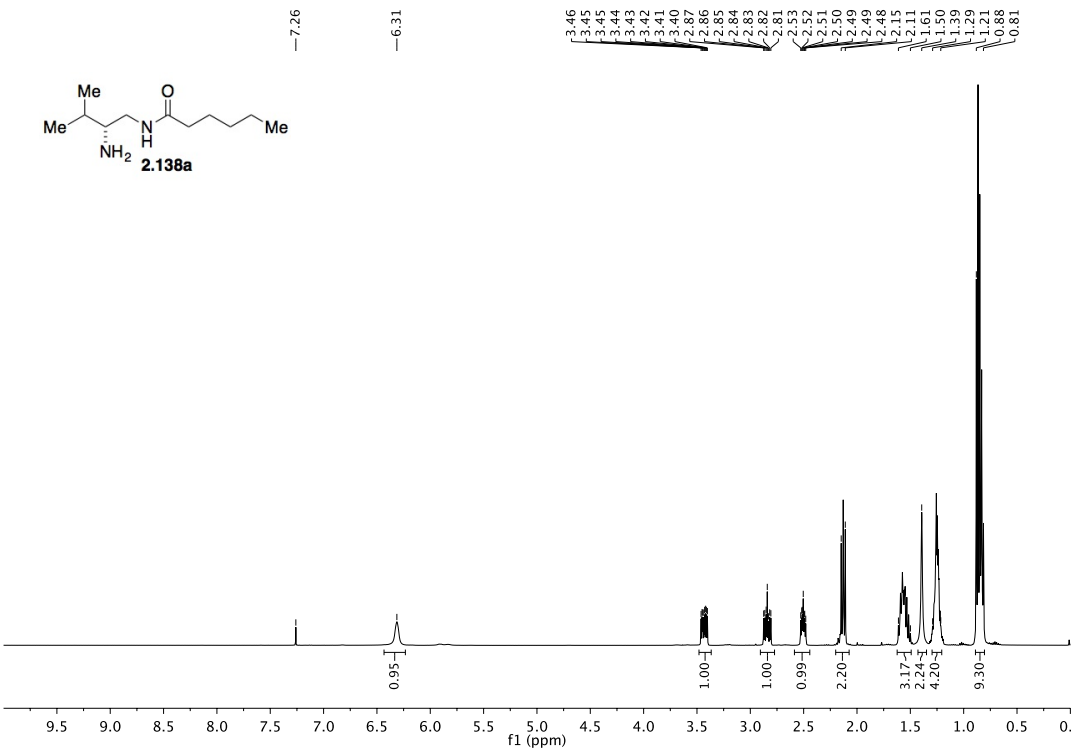
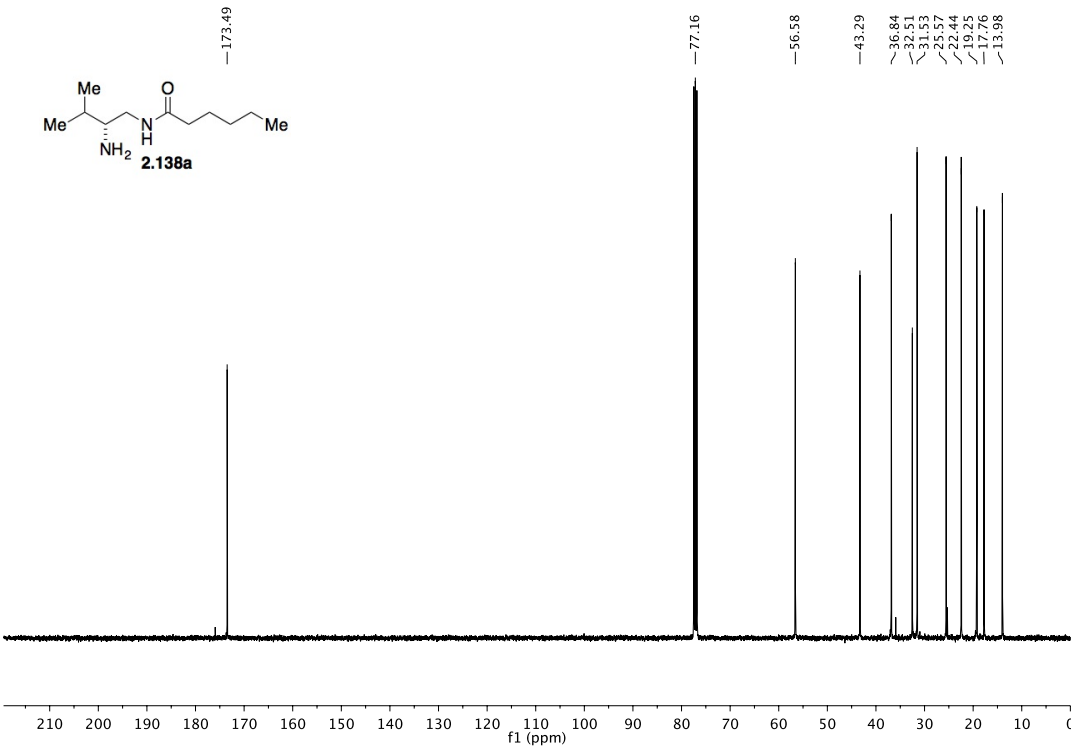
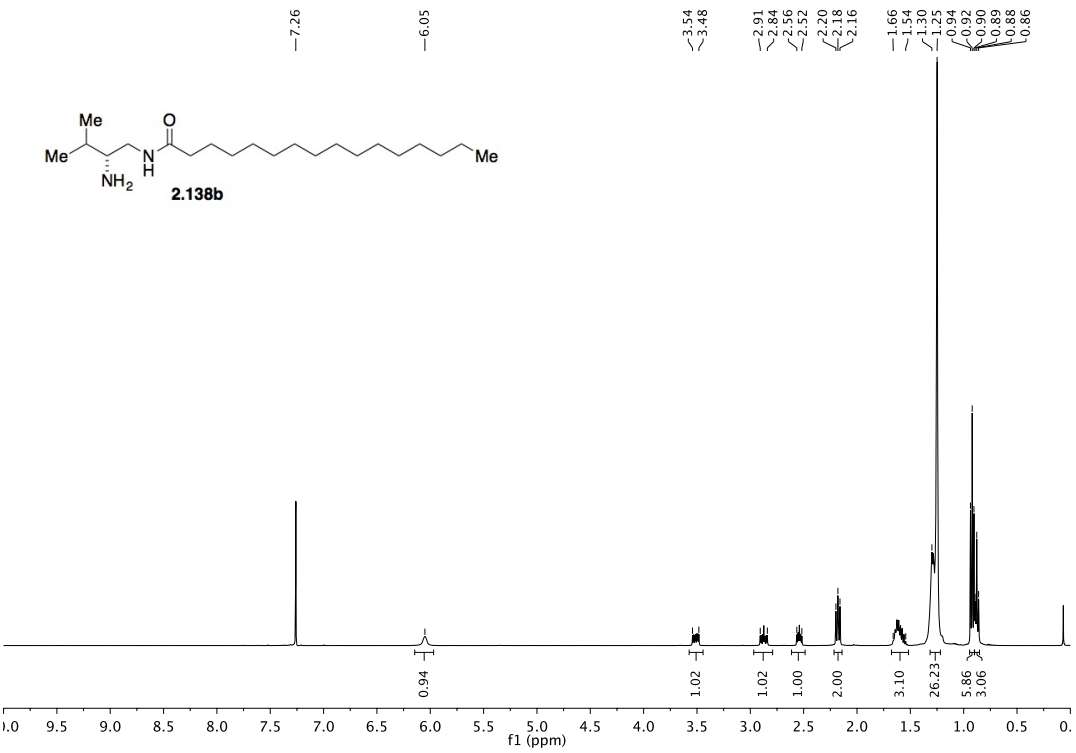
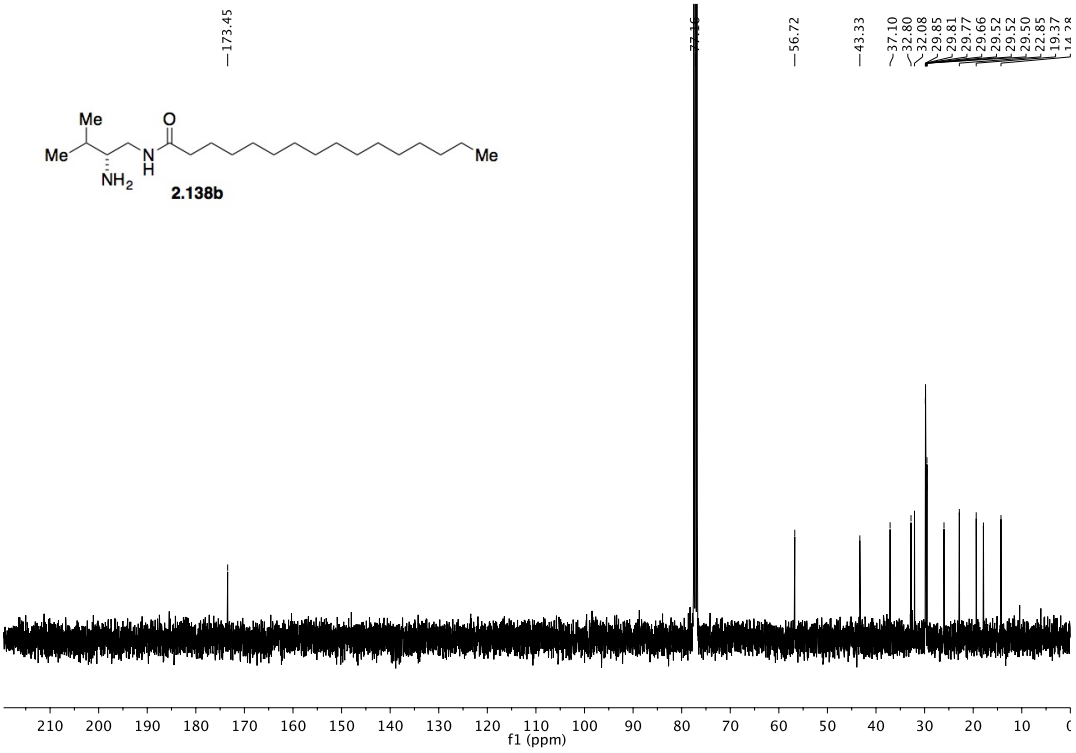
7.39
7.34
7.32
7.31
7.26
5.92
4.92
4.89
4.42
4.40
4.24
4.22
4.20
3.60
3.53
3.45
3.37
3.30
3.29
3.28
3.27
3.26
3.25
1.93
1.84
1.76
0.98
0.96
0.95
0.94
2.18
2.19
2.22
2.23
0.85
0.89
2.08
1.12
1.01
0.96
0.98
3.00
1.21
2.89
2.96
f1 (ppm)

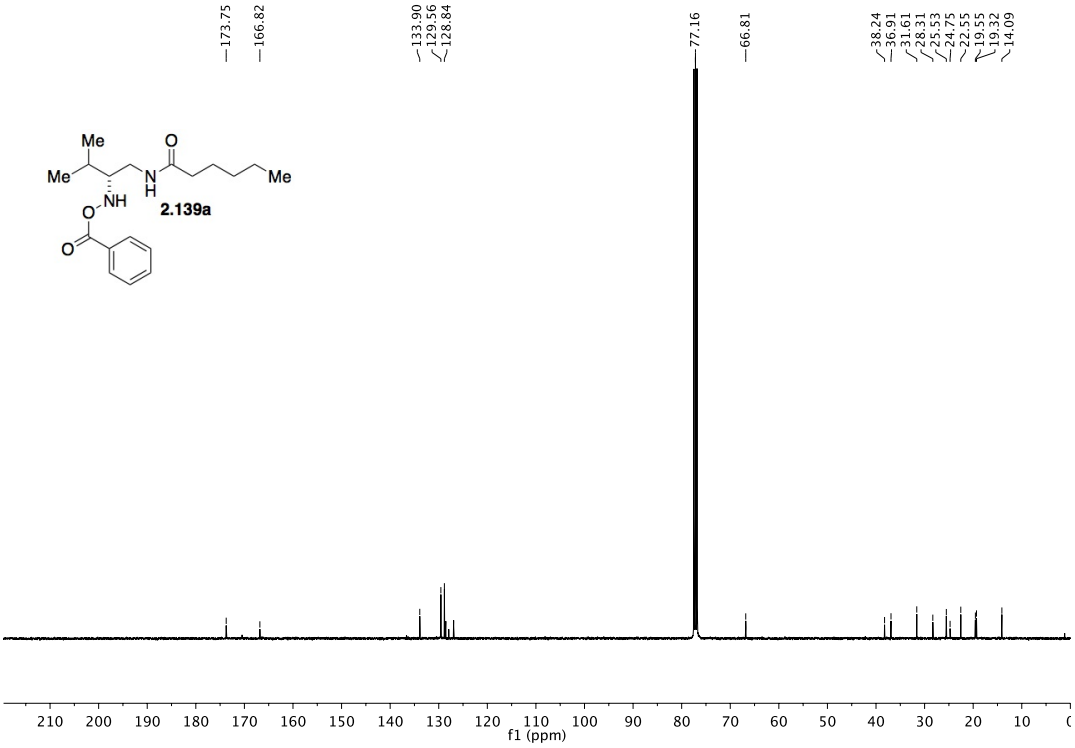

Me
Me
O
N
H
Me
NH
Fmoc
2.137c
171.07
157.51
143.99
143.91
141.46
127.88
127.86
127.22
125.20
125.11
120.14
120.13
77.16
66.93
57.02
47.39
42.64
30.87
23.37
19.38
18.32
f1 (ppm)

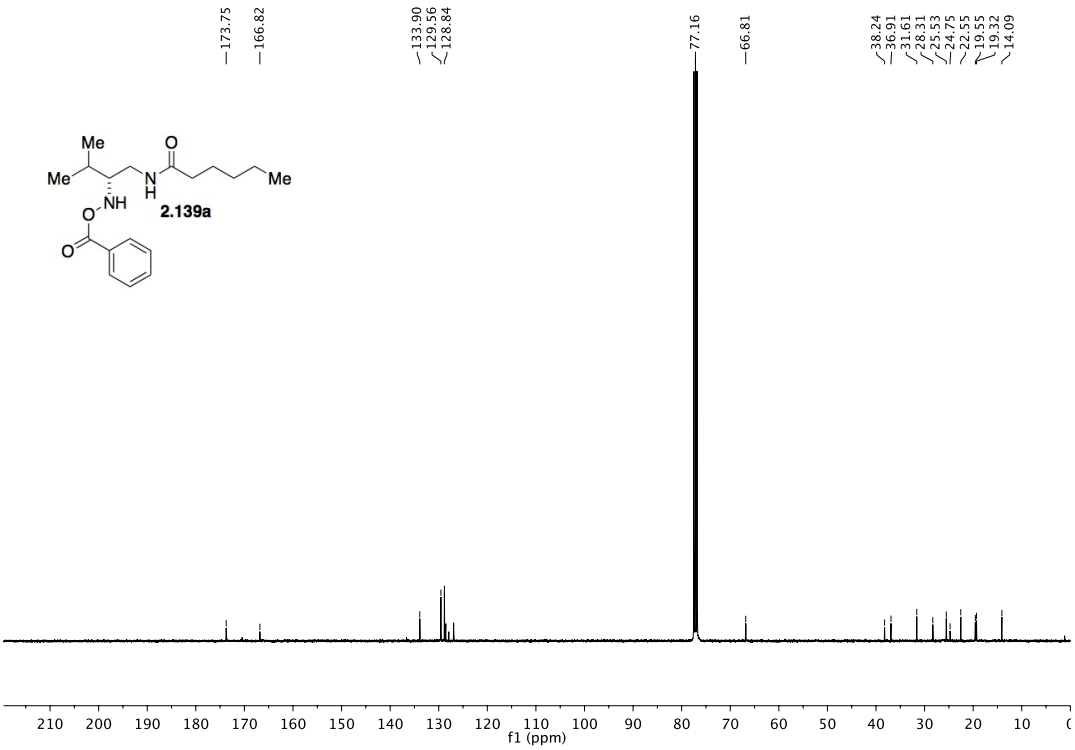

7.26
6.31
3.46
3.45
3.45
3.44
3.43
3.42
3.41
3.40
2.87
2.86
2.85
2.84
2.83
2.82
2.81
2.53
2.52
2.51
2.50
2.49
2.49
2.48
2.15
2.11
1.61
1.50
1.39
1.29
1.21
0.88
0.81
Me
Me
O
N
H
NH2
Me
2.138a
0.95
1.00
1.00
0.99
2.20
3.17
2.24
4.20
9.30
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

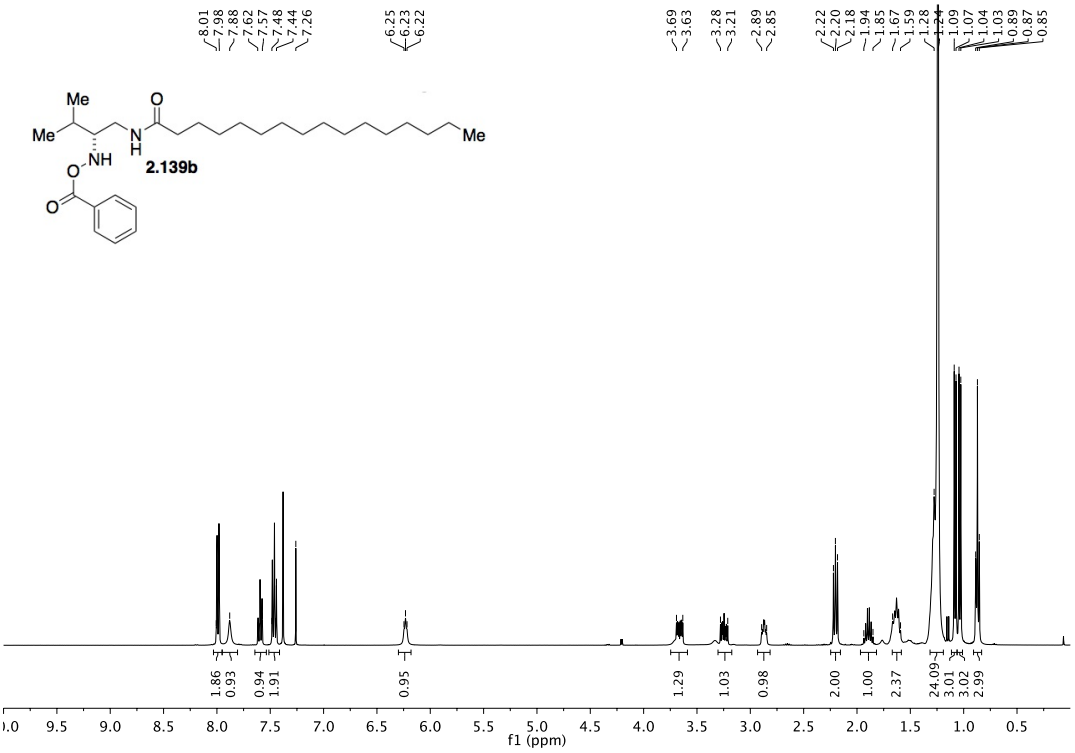

173.49
77.16
56.58
43.29
36.84
32.51
31.53
25.57
22.44
19.25
17.76
13.98
Me
Me
O
N
H
NH2
Me
2.138a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

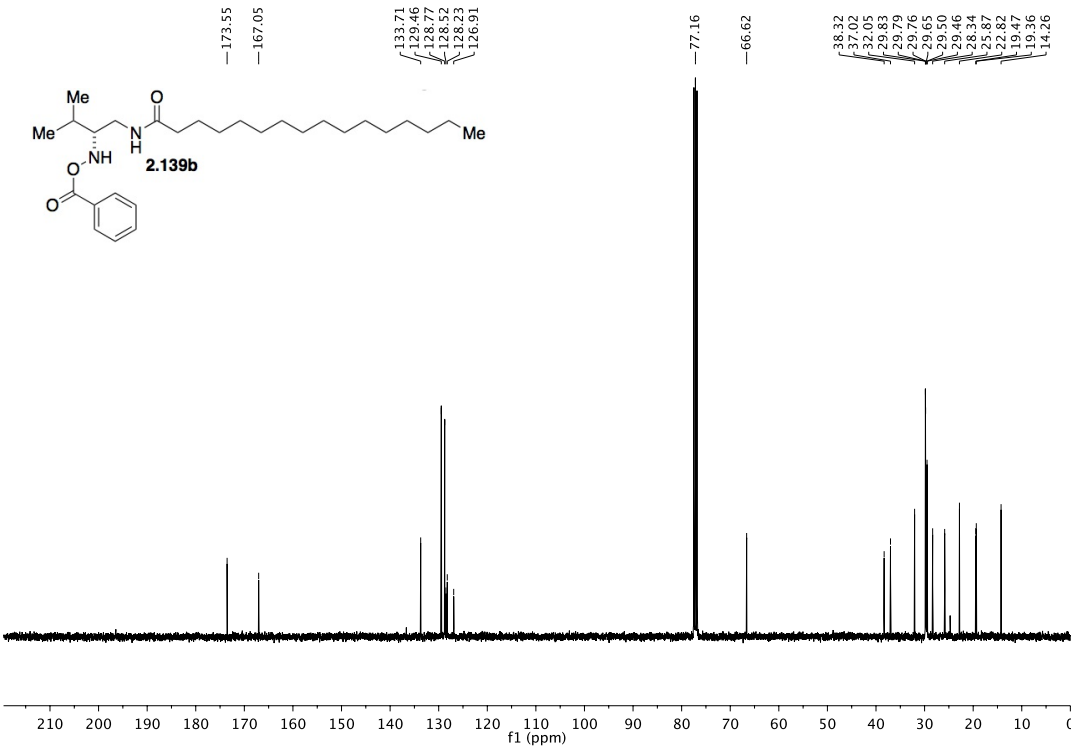

7.26
6.05
3.54
3.48
2.91
2.84
2.56
2.52
2.20
2.18
2.16
1.66
1.54
1.30
1.25
0.94
0.92
0.90
0.89
0.88
0.86
Me
Me
O
N
H
NH2
Me
2.138b
0.94
1.02
1.02
1.00
2.00
3.10
26.23
5.86
3.06
f1 (ppm)

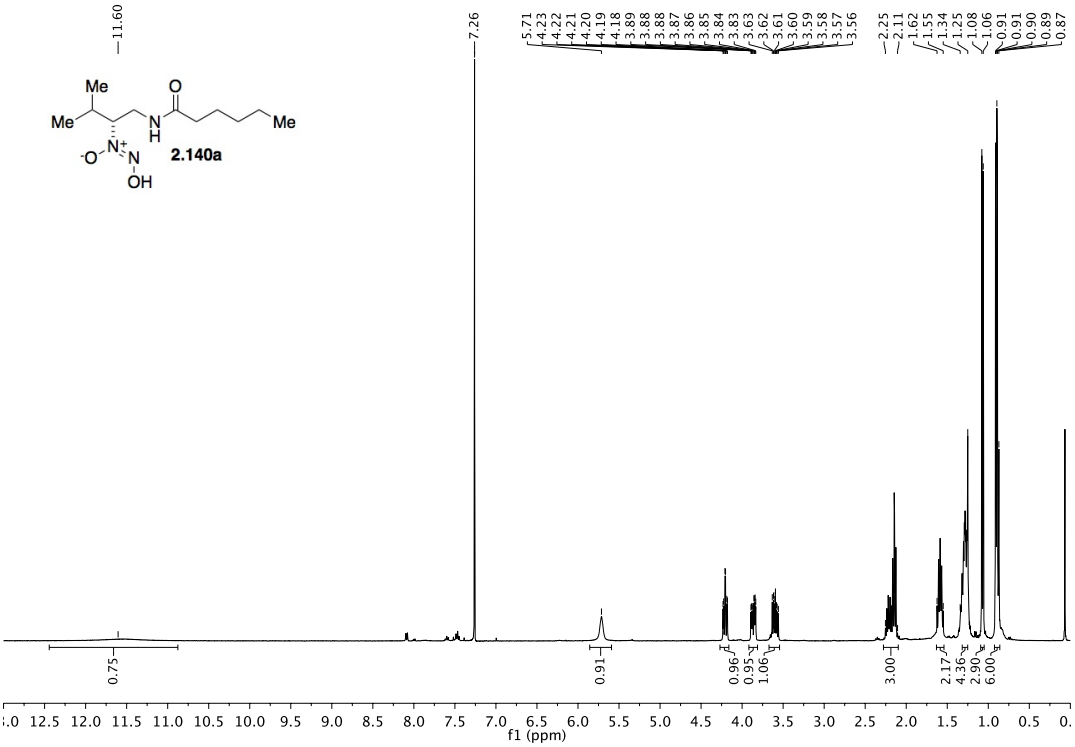

173.45
56.72
43.33
37.10
32.80
32.08
29.85
29.81
29.77
29.66
29.52
29.52
29.50
22.85
19.37
Me
Me
O
N
H
NH2
Me
2.138b
f1 (ppm)

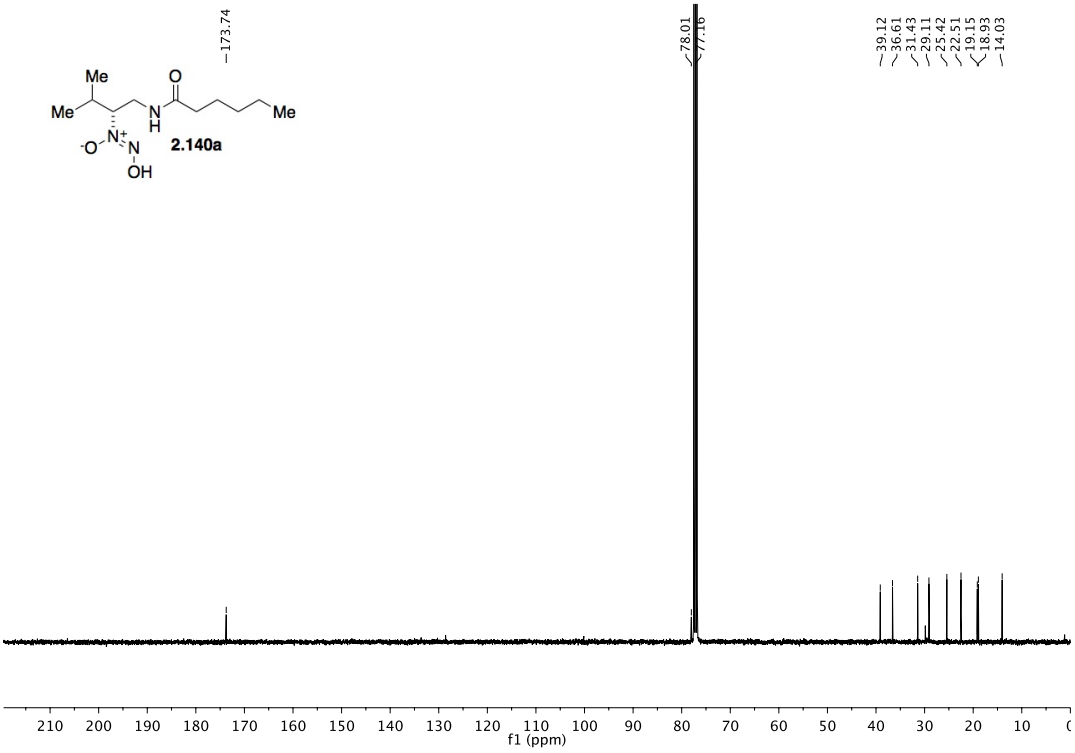

173.75
166.82
133.90
129.56
128.84
77.16
66.81
38.24
36.91
31.61
28.31
25.53
24.75
22.55
19.55
19.32
14.09
Me
Me
N
H
O
Me
NH
O
O
2.139a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

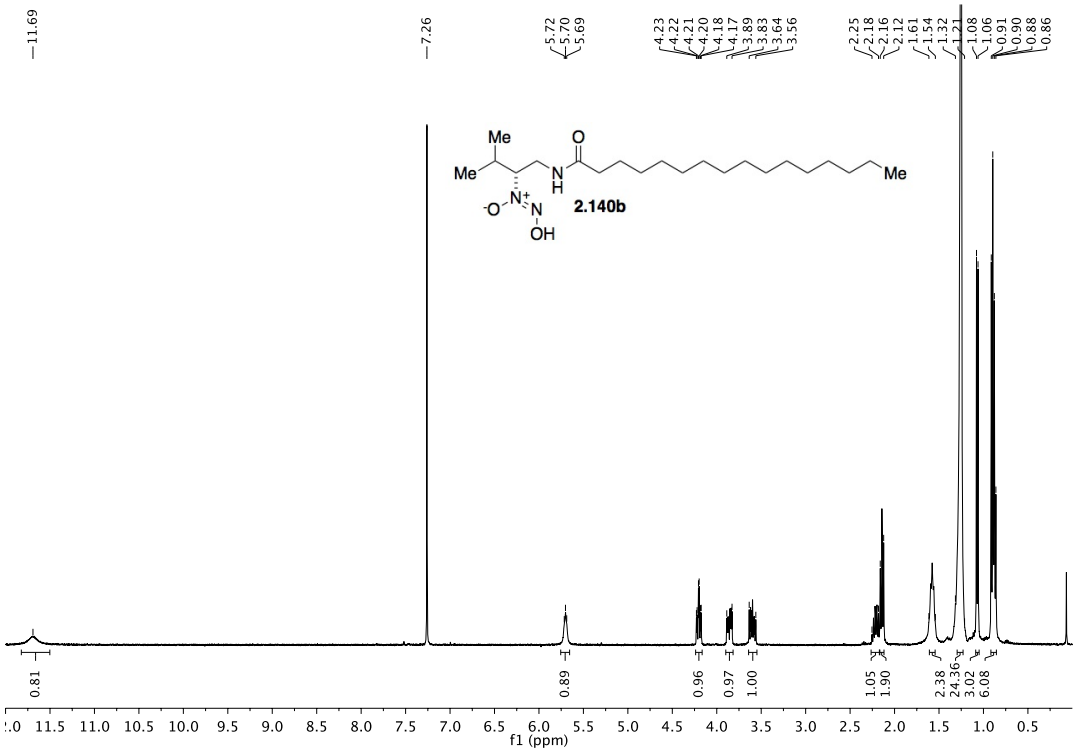

173.75
166.82
133.90
129.56
128.84
77.16
66.81
38.24
36.91
31.61
28.31
25.53
24.75
22.55
19.55
19.32
14.09
Me
Me
N
H
O
Me
NH
O
O
2.139a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

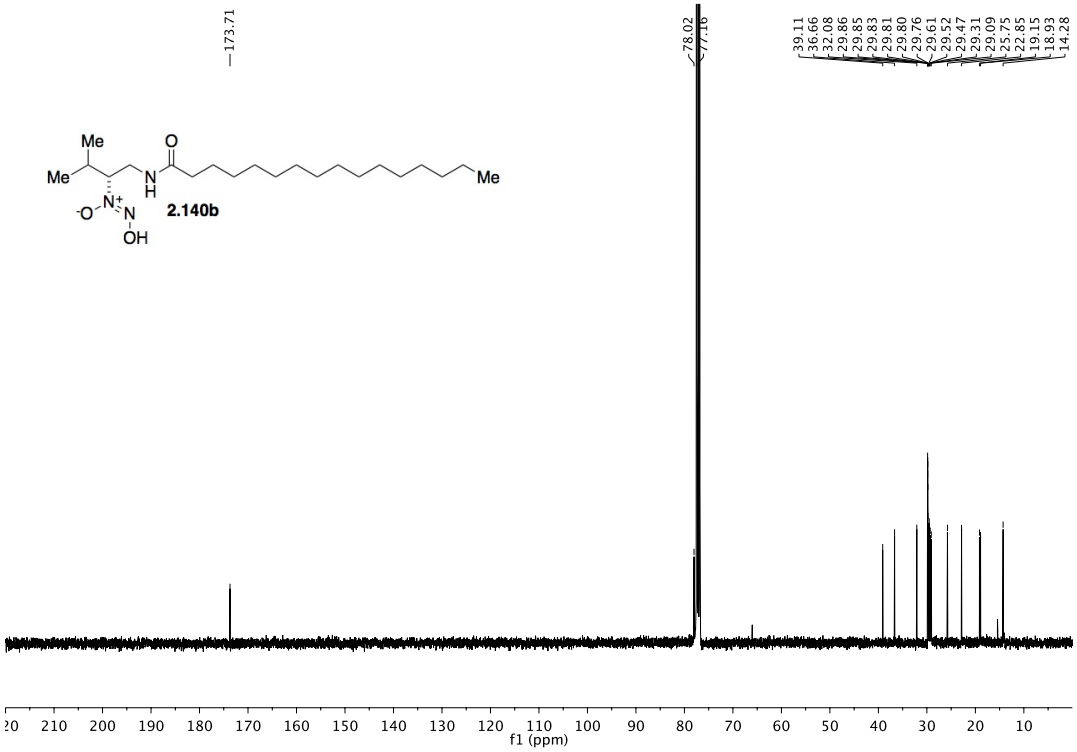

8.01
7.98
7.88
7.62
7.57
7.48
7.44
7.26
6.25
6.23
6.22
3.69
3.63
3.28
3.21
2.89
2.85
2.22
2.20
2.18
1.94
1.85
1.67
1.59
1.28
1.24
1.09
1.07
1.04
1.03
0.89
0.87
0.85
Me
Me
O
N
H
NH
O
O
Me
2.139b
1.86
0.93
0.94
1.91
0.95
1.29
1.03
0.98
2.00
1.00
2.37
24.09
3.01
3.02
2.99
f1 (ppm)

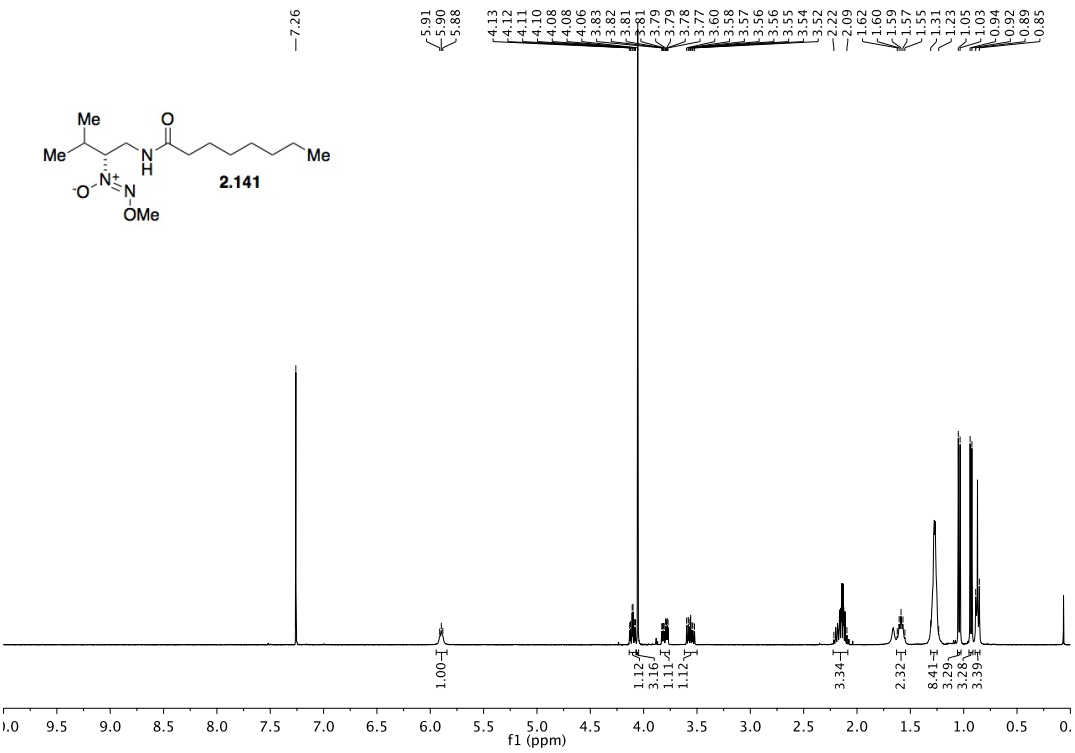

173.55
167.05
133.71
129.46
128.77
128.52
128.23
126.91
77.16
66.62
38.32
37.02
32.05
29.83
29.79
29.76
29.65
29.50
29.46
28.34
25.87
22.82
19.47
19.36
14.26
Me
Me
O
N
H
NH
O
O
Me
2.139b
f1 (ppm)

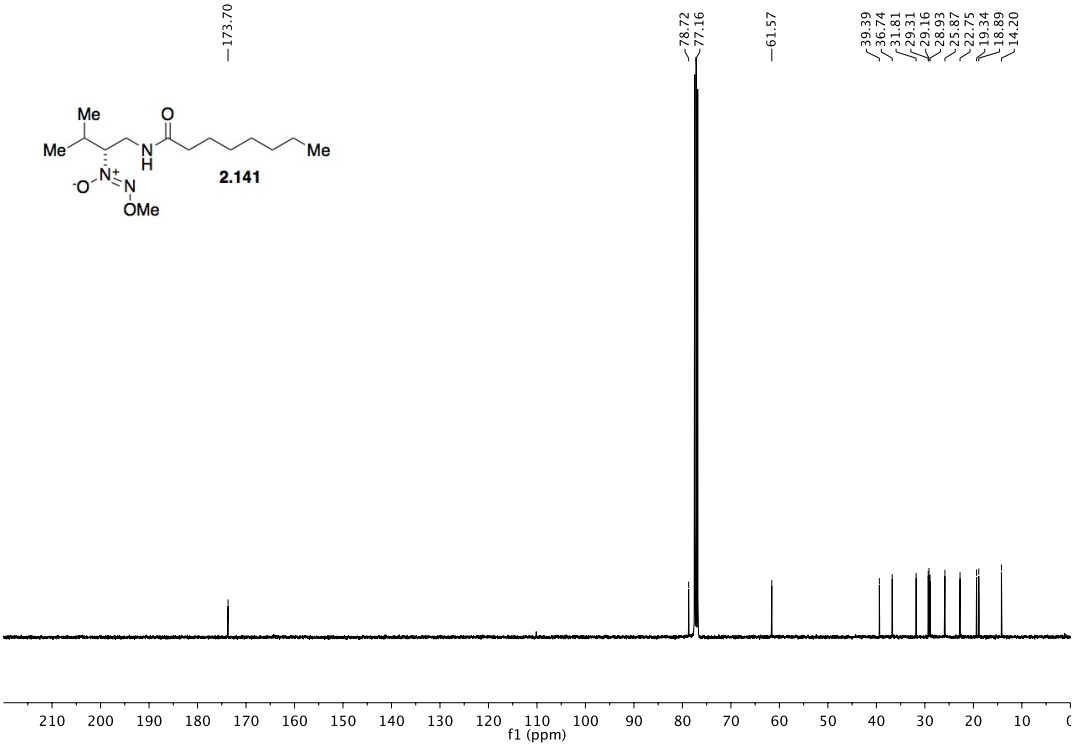

11.60
7.26
5.71
4.23
4.22
4.21
4.20
4.19
4.18
3.89
3.88
3.87
3.86
3.85
3.84
3.83
3.63
3.62
3.61
3.60
3.59
3.58
3.57
3.56
2.25
2.11
1.62
1.55
1.34
1.25
1.08
1.06
0.91
0.91
0.90
0.89
0.87
Me
Me
O
N
H
Me
N+
O
N
OH
2.140a
0.75
0.91
0.96
0.95
1.06
3.00
2.17
4.36
2.90
6.00
f1 (ppm)


173.74
78.01
77.16
39.12
36.61
31.43
29.11
25.42
22.51
19.15
18.93
14.03
Me
Me
O
N
H
Me
N+
O
N
OH
2.140a
f1 (ppm)

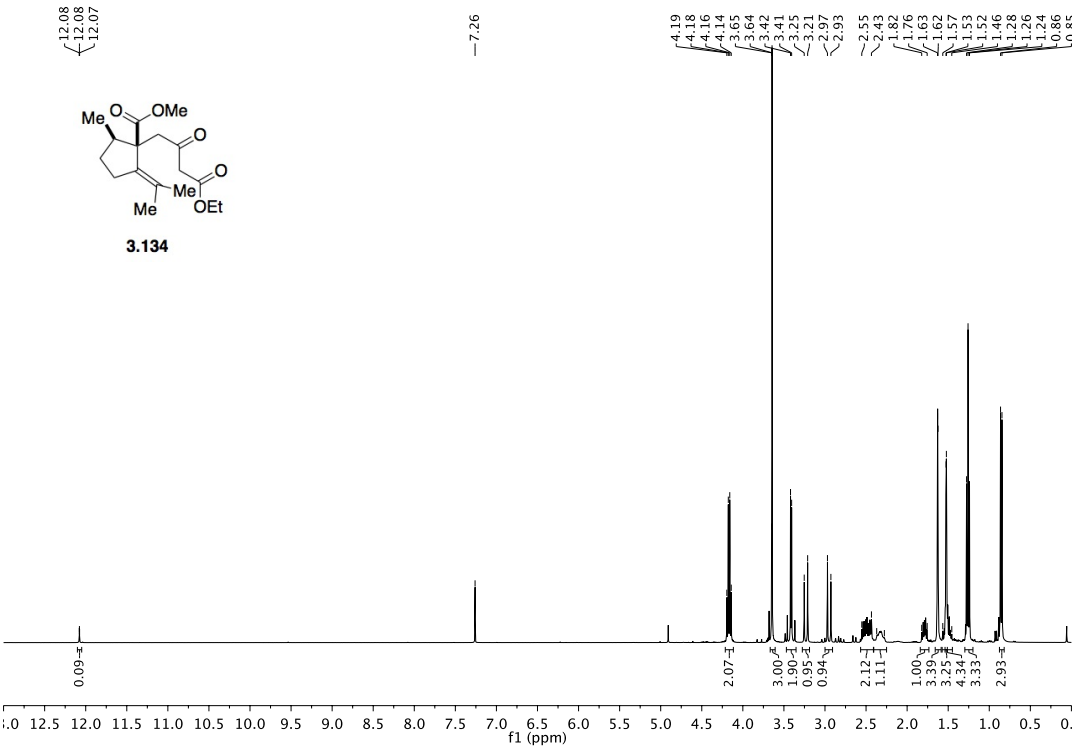

11.69
7.26
5.72
5.70
5.69
4.23
4.22
4.21
4.20
4.18
4.17
3.89
3.83
3.64
3.56
2.25
2.18
2.16
2.12
1.61
1.54
1.32
1.21
1.08
1.06
0.91
0.90
0.88
0.86
Me
O
Me
N
H
Me
N+
-O
N
OH
2.140b
0.81
0.89
0.96
0.97
1.00
1.05
1.90
2.38
24.36
3.02
6.08
f1 (ppm)

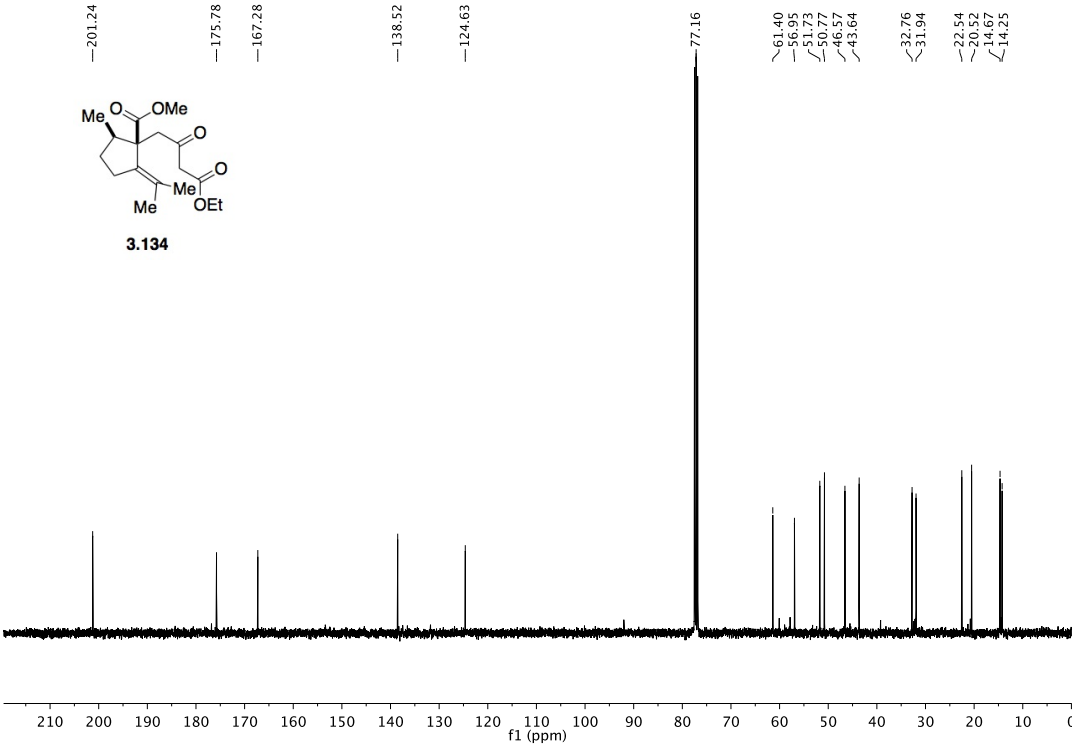

173.71
78.02
77.16
39.11
36.66
32.08
29.86
29.85
29.83
29.81
29.80
29.76
29.61
29.52
29.47
29.31
29.09
25.75
22.85
19.15
18.93
14.28
Me
O
Me
N
H
Me
N+
-O
N
OH
2.140b
f1 (ppm)

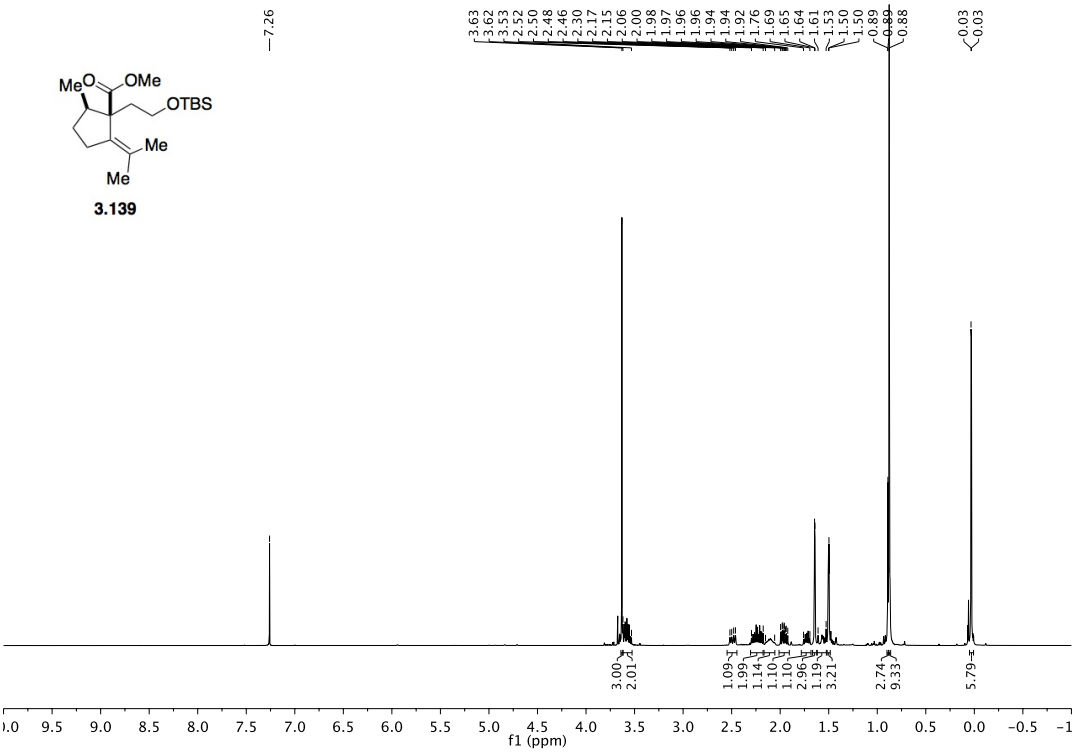

7.26
5.91
5.90
5.88
4.13
4.12
4.11
4.10
4.08
4.08
4.06
3.83
3.82
3.81
3.81
3.79
3.79
3.78
3.77
3.60
3.58
3.57
3.56
3.56
3.55
3.54
3.52
2.22
2.09
1.62
1.60
1.59
1.57
1.55
1.31
1.23
1.05
1.03
0.94
0.92
0.89
0.85
Me
Me
O
N
H
Me
N+
O-
N
OMe
2.141
1.00
1.12
3.16
1.11
1.12
3.34
2.32
8.41
3.29
3.28
3.39
f1 (ppm)

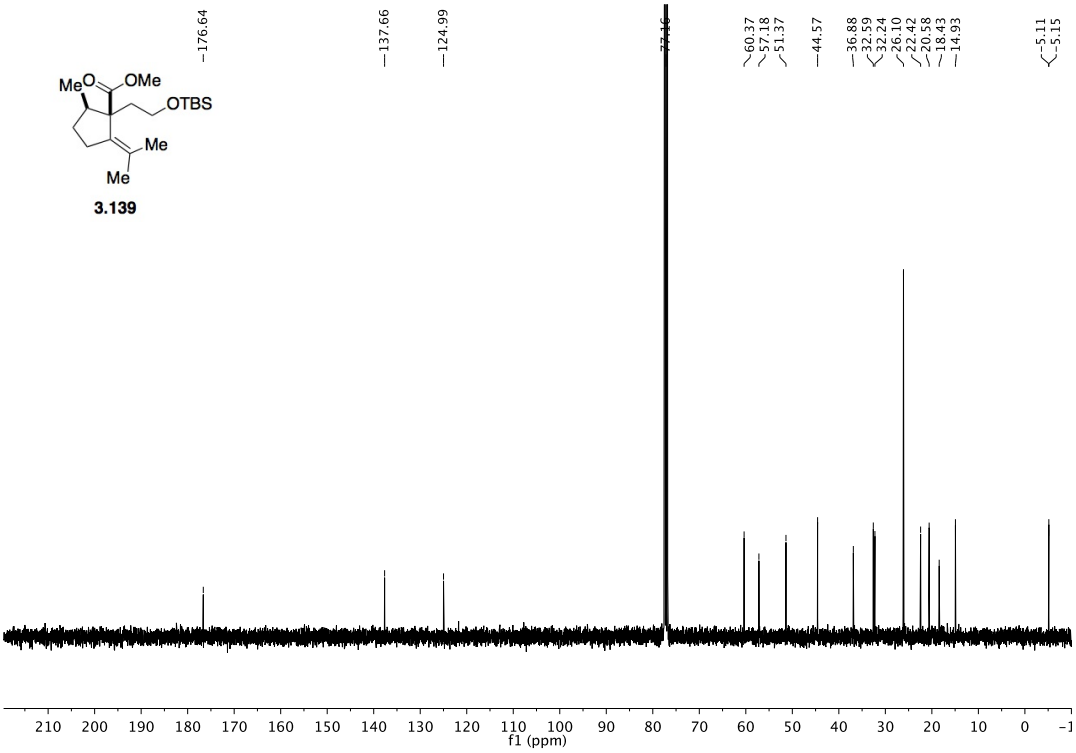

173.70
78.72
77.16
61.57
39.39
36.74
31.81
29.31
29.16
28.93
25.87
22.75
19.34
18.89
14.20
Me
Me
O
N
H
Me
N+
O-
N
OMe
2.141
f1 (ppm)

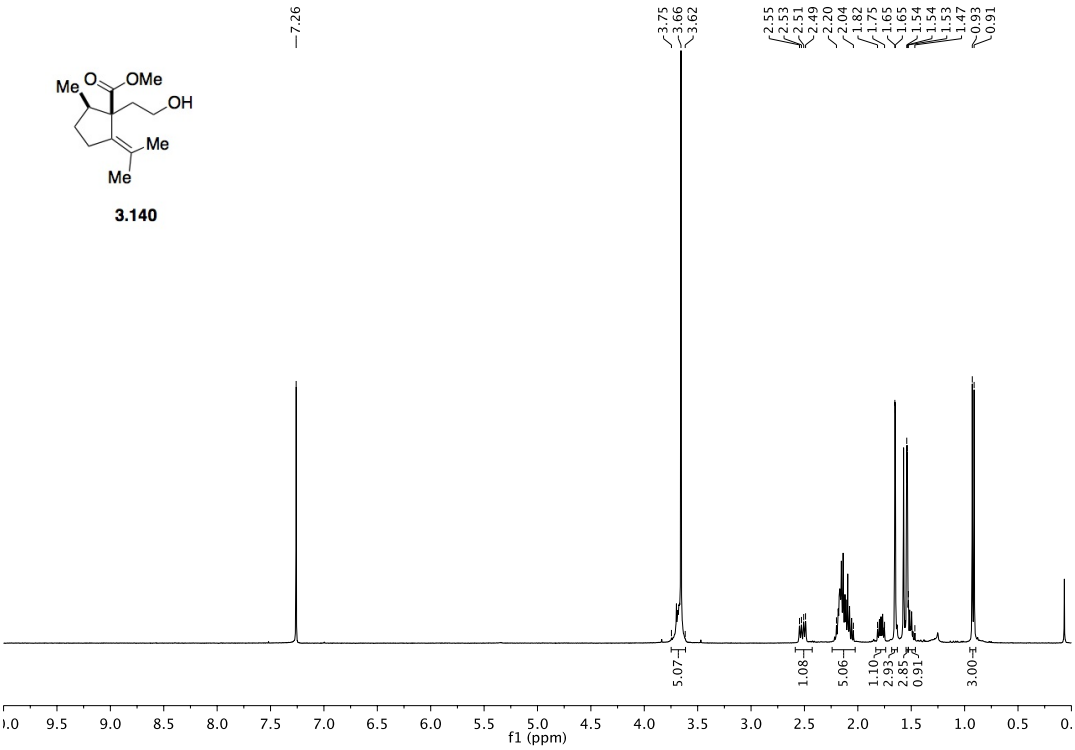
8.3.2 Synthetic Studies Towards (2*R*)-Hydroxynorneomajucin

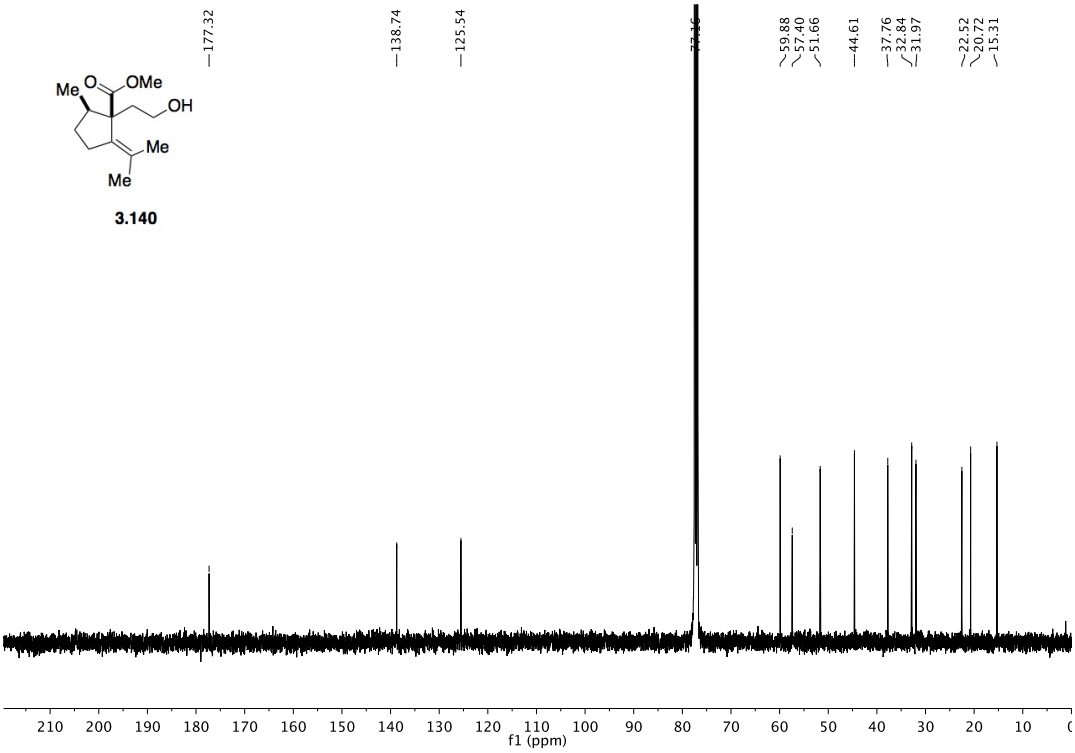


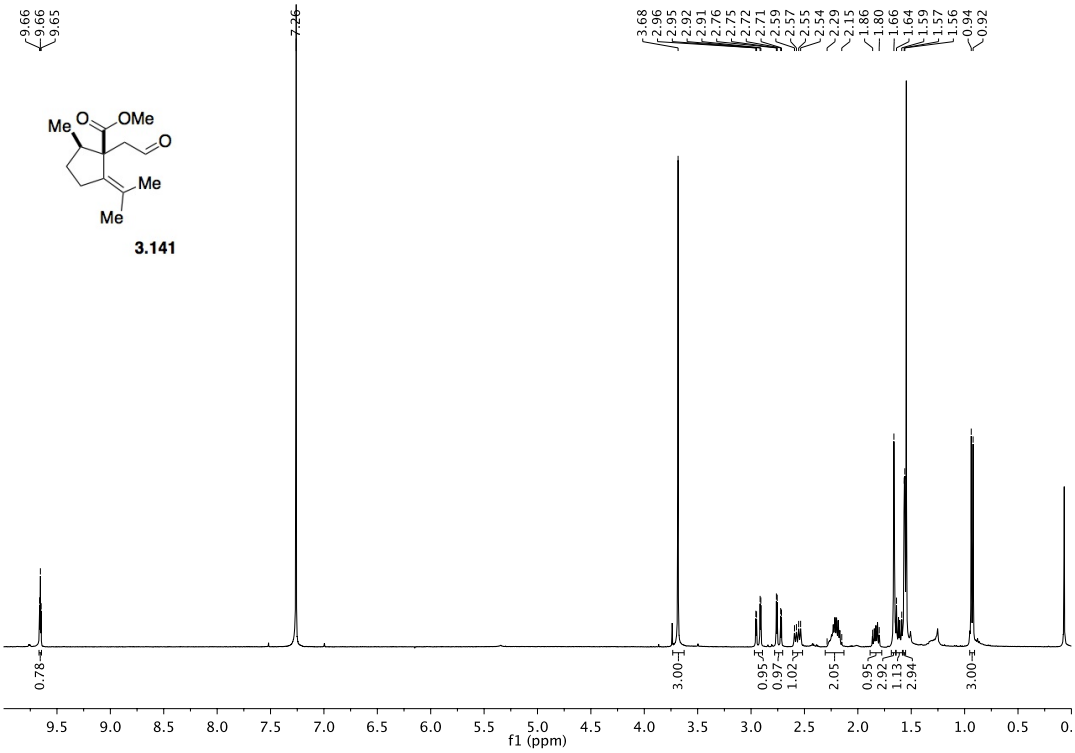


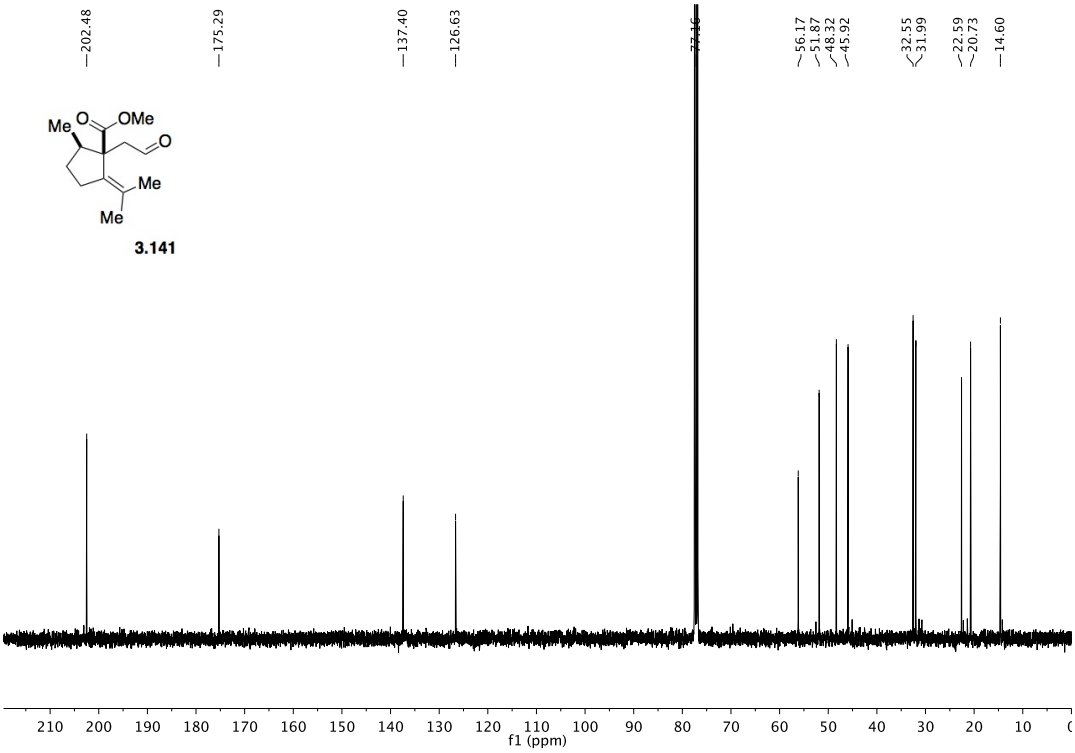

Me
O
OMe
OTBS
Me
Me
3.139
7.26
3.63
3.62
3.53
2.52
2.50
2.48
2.46
2.30
2.17
2.15
2.06
2.00
1.98
1.97
1.96
1.96
1.94
1.94
1.92
1.76
1.69
1.65
1.64
1.61
1.53
1.50
1.50
0.89
0.89
0.88
0.03
0.03
3.00
2.01
1.09
1.99
1.14
1.10
1.10
2.96
1.19
3.21
2.74
9.33
5.79
f1 (ppm)

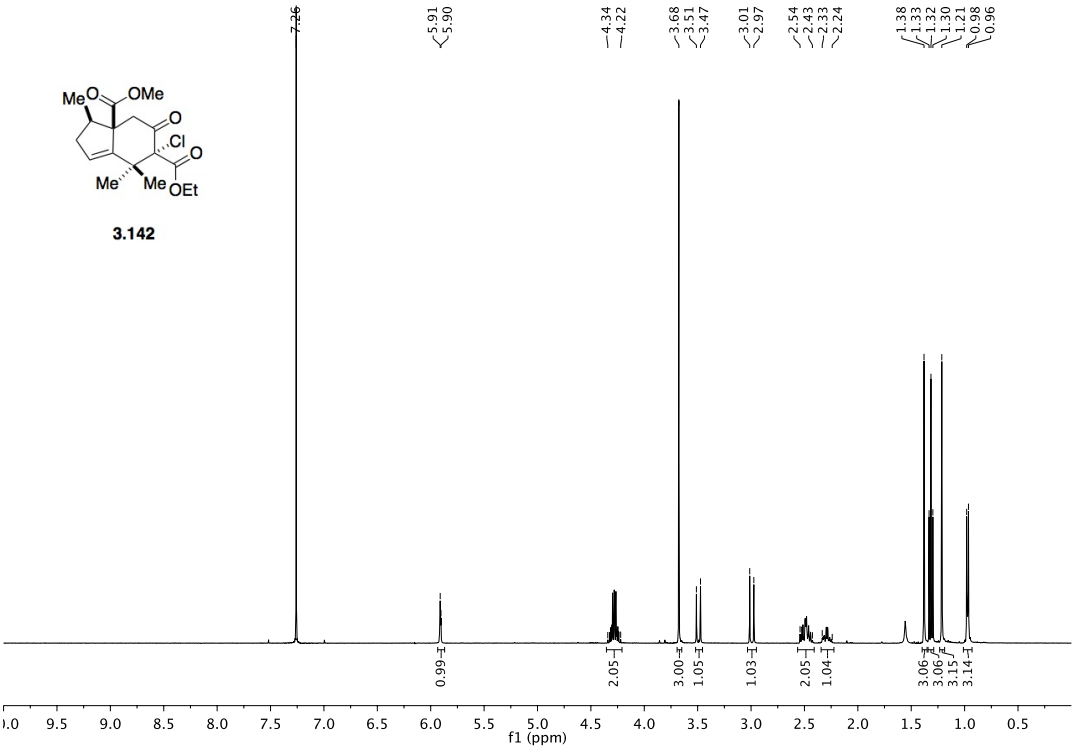

Me
O
OMe
OTBS
Me
Me
3.139
176.64
137.66
124.99
77.16
60.37
57.18
51.37
44.57
36.88
32.59
32.24
26.10
22.42
20.58
18.43
14.93
5.11
5.15
f1 (ppm)

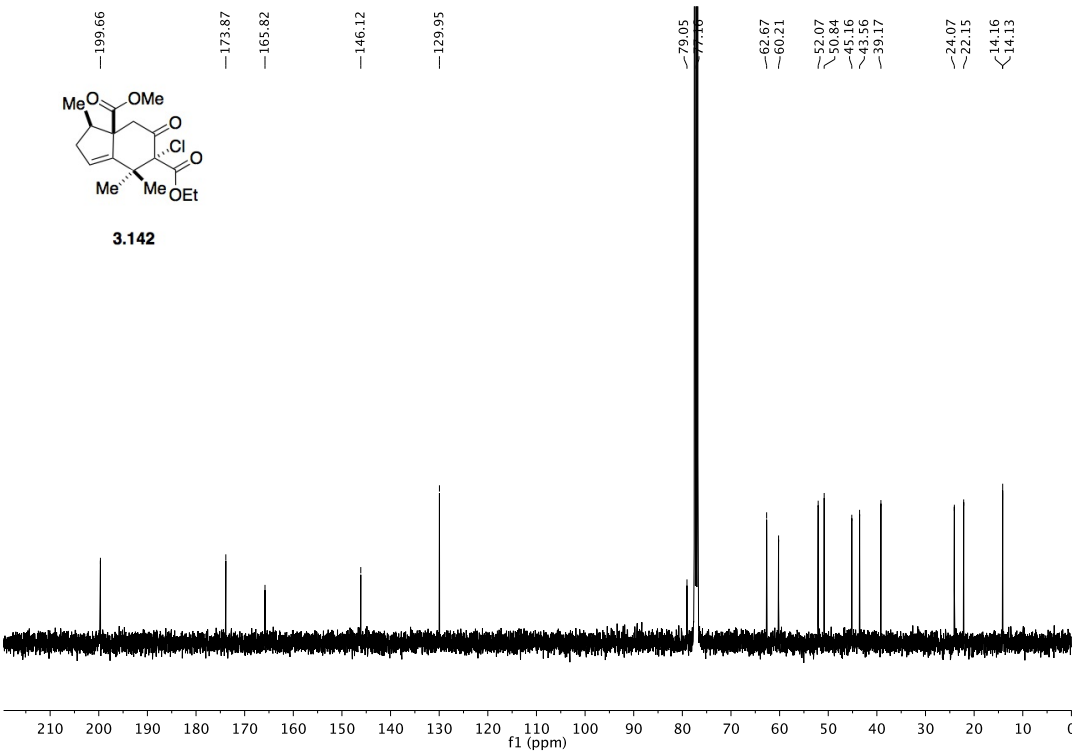

7.26
3.75
3.66
3.62
2.55
2.53
2.51
2.49
2.20
2.04
1.82
1.75
1.65
1.54
1.53
1.47
0.93
0.91
Me
O
OMe
OH
Me
Me
3.140
5.07
1.08
5.06
1.10
2.93
2.85
0.91
3.00
f1 (ppm)

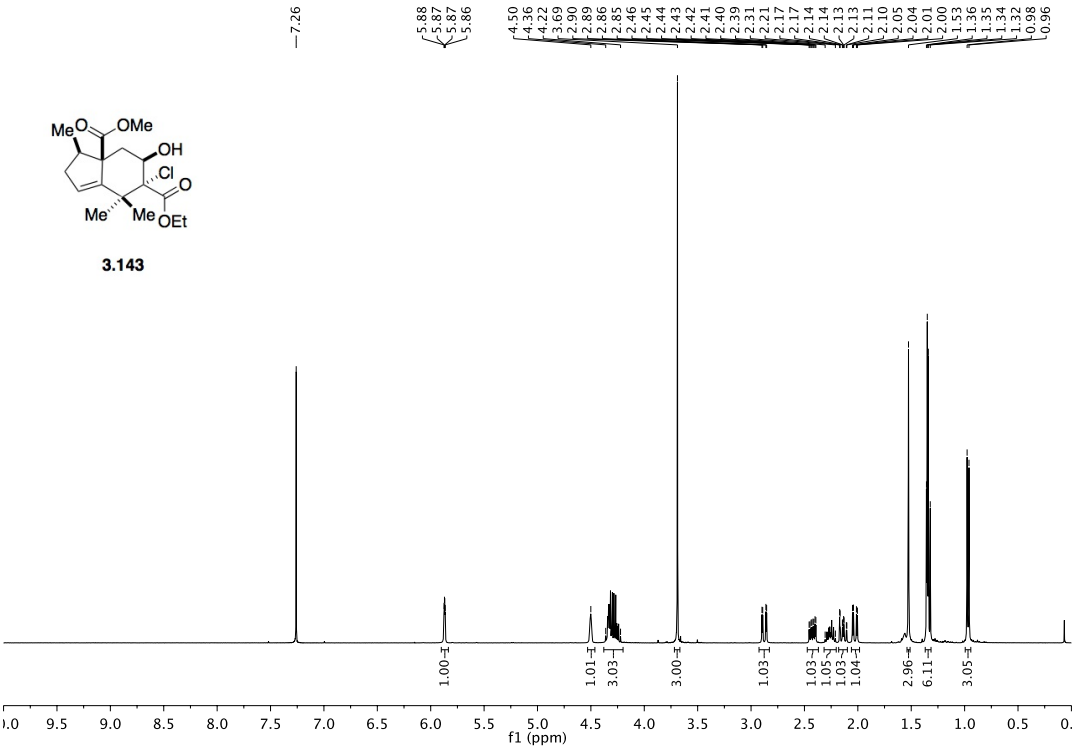

177.32
138.74
125.54
59.88
57.40
51.66
44.61
37.76
32.84
31.97
22.52
20.72
15.31
Me
O
OMe
OH
Me
Me
3.140
f1 (ppm)

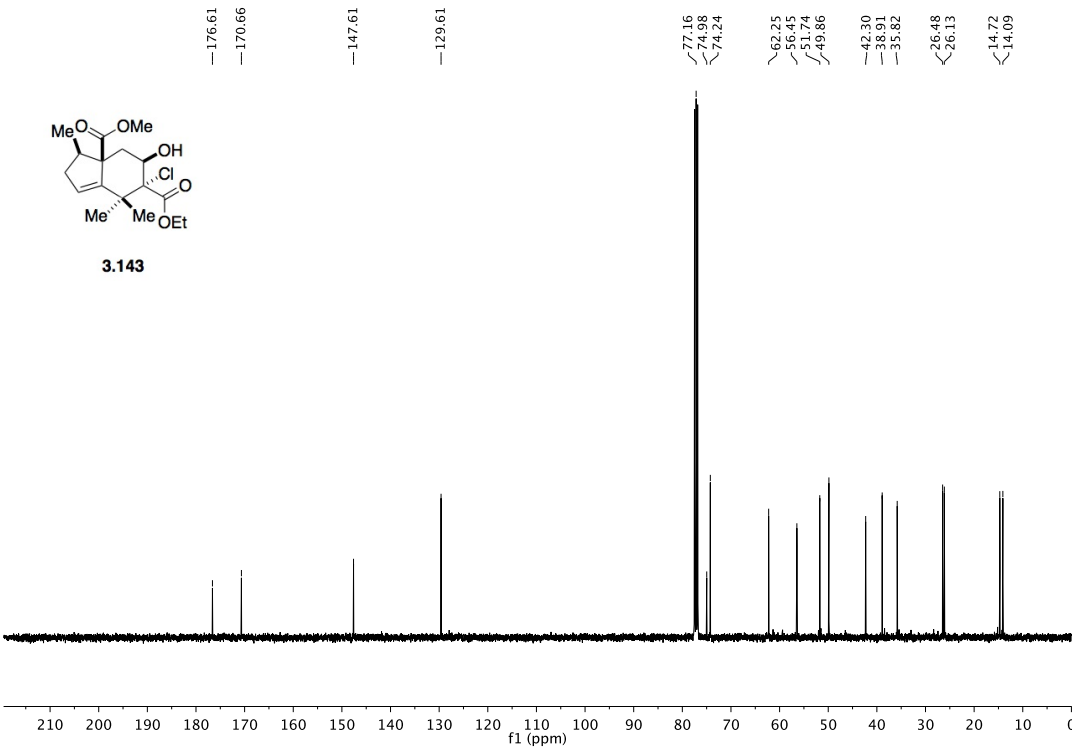

9.66
9.66
9.65
7.26
3.68
2.96
2.95
2.92
2.91
2.76
2.75
2.72
2.71
2.59
2.57
2.55
2.54
2.29
2.15
1.86
1.80
1.66
1.64
1.59
1.57
1.56
0.94
0.92
Me
O
OMe
O
Me
Me
3.141
0.78
3.00
0.95
0.97
1.02
2.05
0.95
2.92
1.13
2.94
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

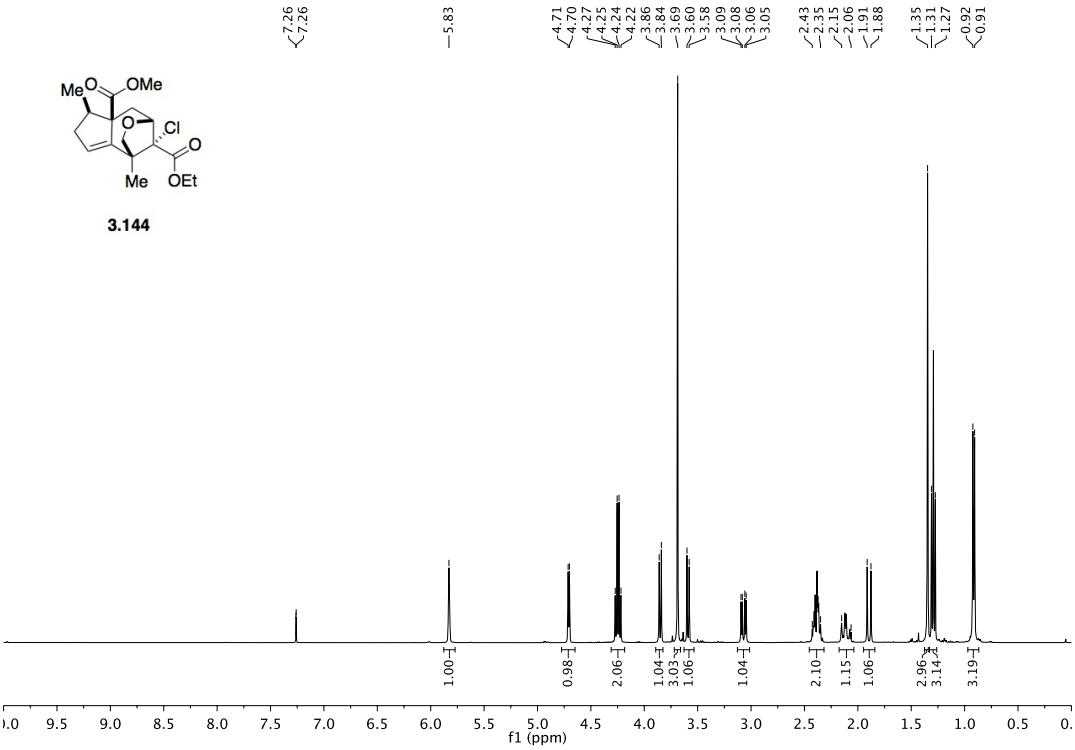

202.48
175.29
137.40
126.63
77.16
56.17
51.87
48.32
45.92
32.55
31.99
22.59
20.73
14.60
Me
O
OMe
O
Me
Me
3.141
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

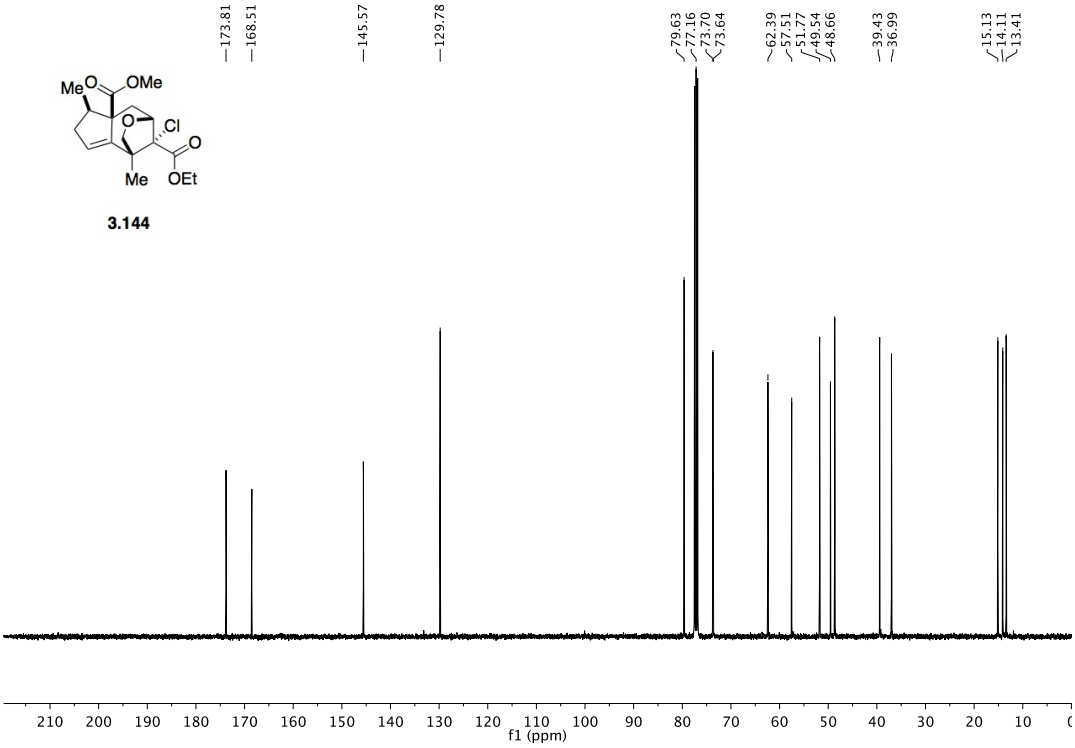

7.26
5.91
5.90
4.34
4.22
3.68
3.51
3.47
3.01
2.97
2.54
2.43
2.33
2.24
1.38
1.33
1.32
1.30
1.21
0.98
0.96
0.99
2.05
3.00
1.05
1.03
2.05
1.04
3.06
3.06
3.15
3.14
f1 (ppm)

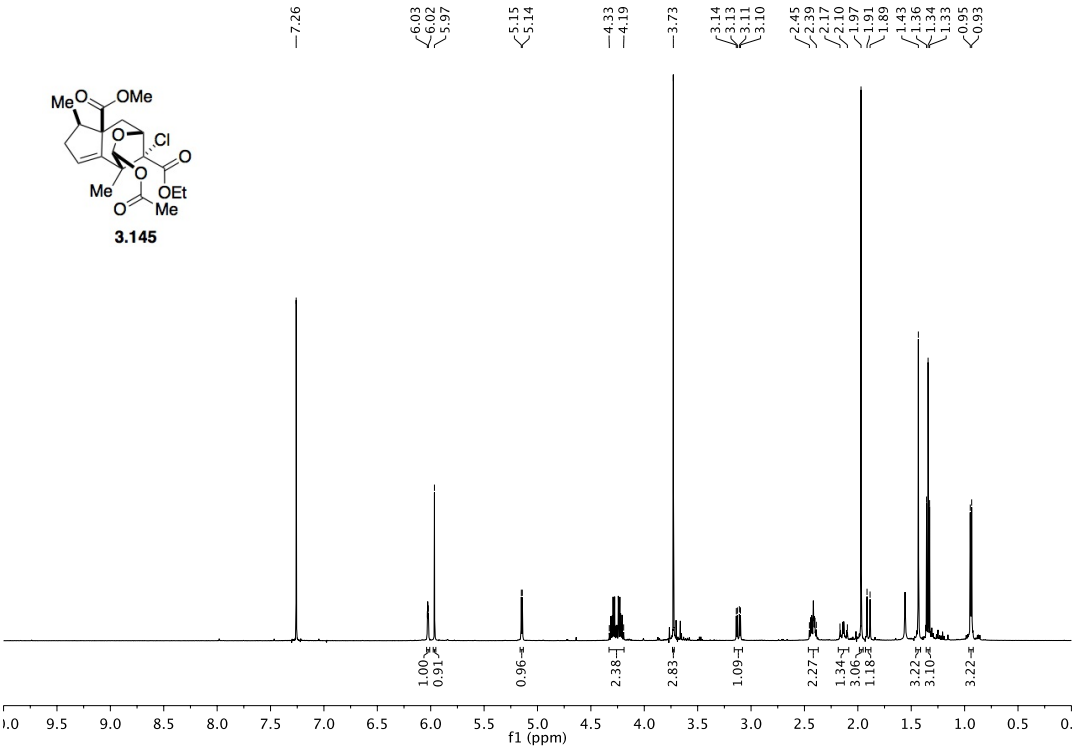

199.66
173.87
165.82
146.12
129.95
79.05
77.16
62.67
60.21
52.07
50.84
45.16
43.56
39.17
24.07
22.15
14.16
14.13
f1 (ppm)

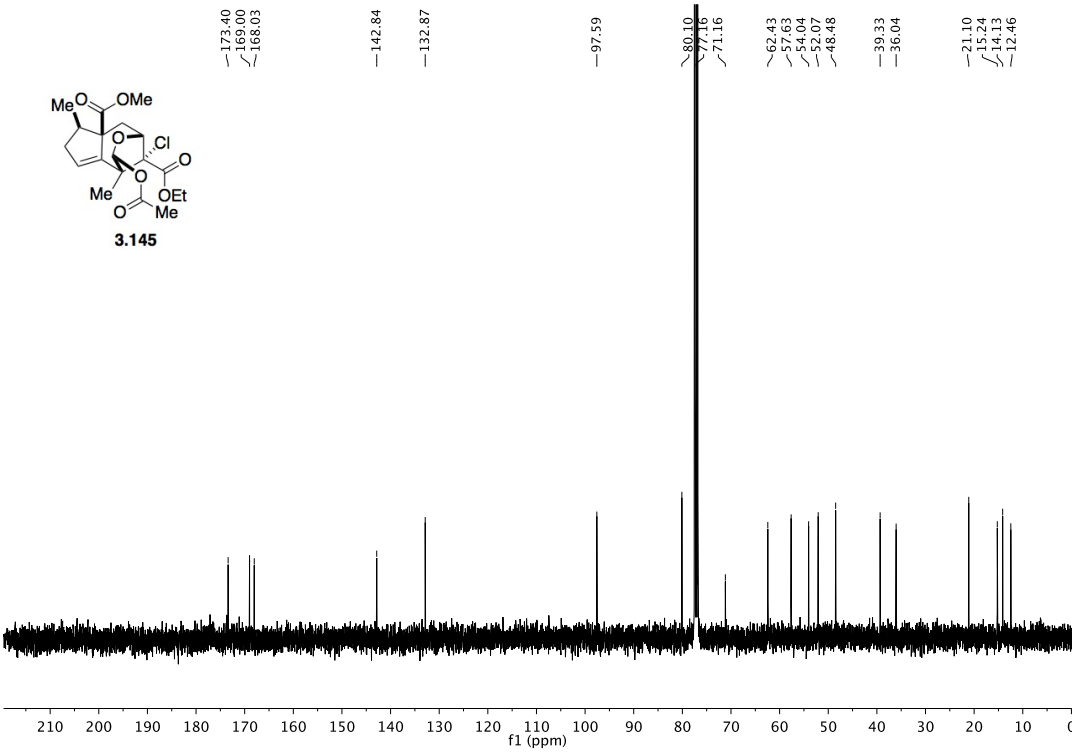

7.26
5.88
5.87
5.87
5.86
4.50
4.36
4.22
3.69
2.90
2.89
2.86
2.85
2.46
2.45
2.44
2.43
2.42
2.41
2.40
2.39
2.31
2.21
2.17
2.17
2.14
2.14
2.13
2.13
2.11
2.10
2.05
2.04
2.01
2.00
1.53
1.36
1.35
1.34
1.32
0.98
0.96
Me
O
OMe
OH
Cl
O
Me
Me
OEt
3.143
1.00
1.01
3.03
3.00
1.03
1.03
1.05
1.03
1.04
2.96
6.11
3.05
f1 (ppm)

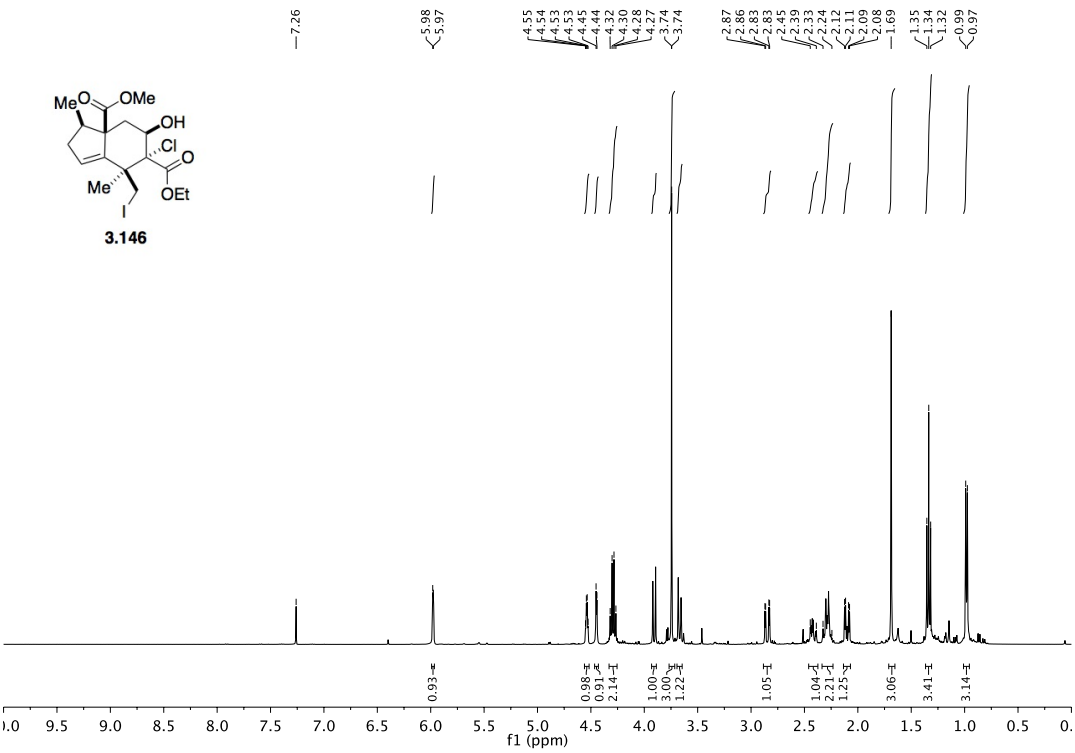

176.61
170.66
147.61
129.61
77.16
74.98
74.24
62.25
56.45
51.74
49.86
42.30
38.91
35.82
26.48
26.13
14.72
14.09
Me
O
OMe
OH
Cl
O
Me
Me
OEt
3.143
f1 (ppm)

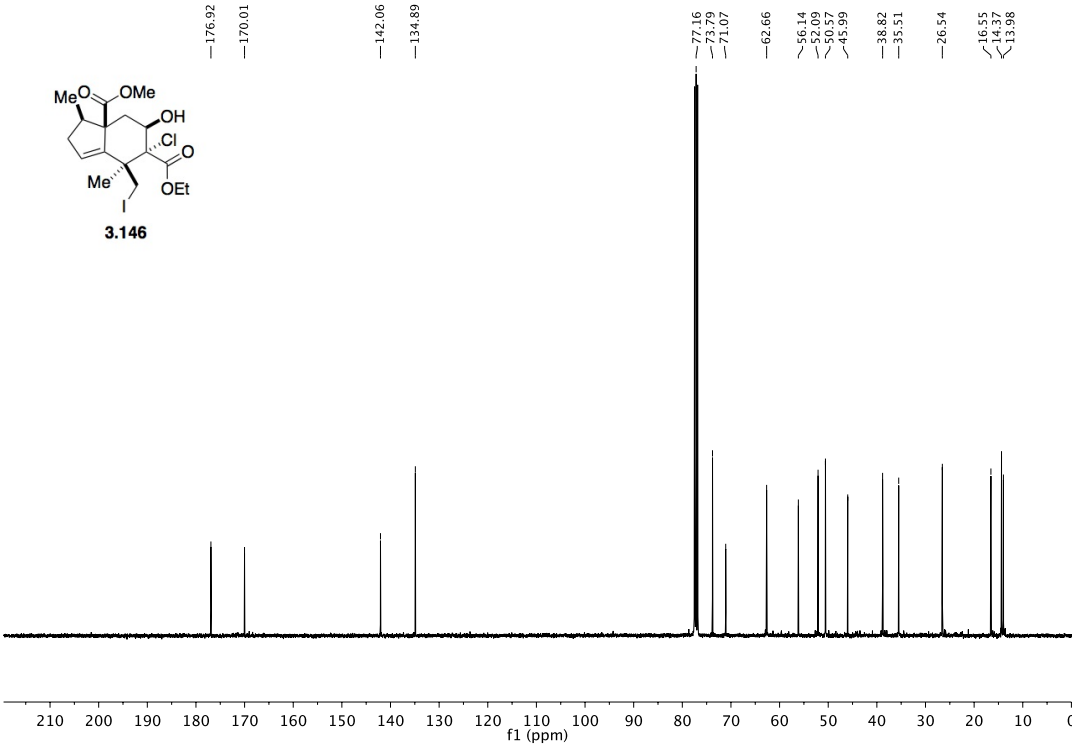

7.26
7.26
5.83
4.71
4.70
4.27
4.25
4.24
4.22
3.86
3.84
3.69
3.60
3.58
3.09
3.08
3.06
3.05
2.43
2.35
2.15
2.06
1.91
1.88
1.35
1.31
1.27
0.92
0.91
Me
OMe
O
Cl
O
Me
OEt
3.144
1.00
0.98
2.06
1.04
3.03
1.06
1.04
2.10
1.15
1.06
2.96
3.14
3.19
f1 (ppm)

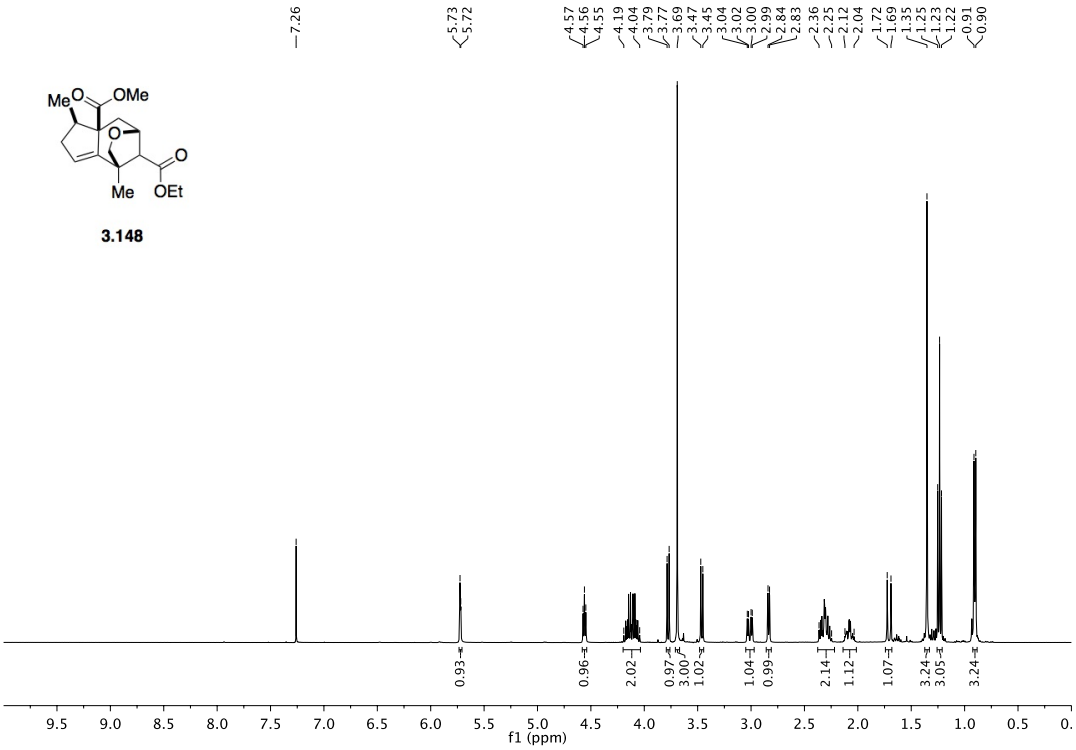

173.81
168.51
145.57
129.78
79.63
77.16
73.70
73.64
62.39
57.51
51.77
49.54
48.66
39.43
36.99
15.13
14.11
13.41
Me
OMe
O
Cl
O
Me
OEt
3.144
f1 (ppm)

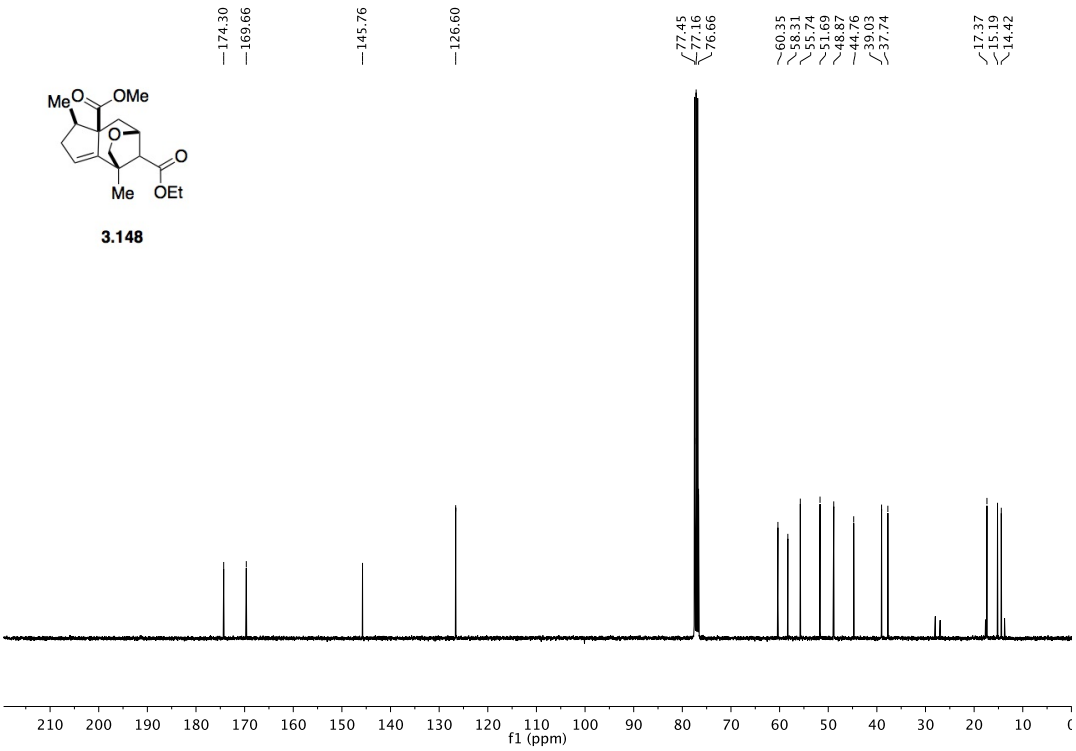

7.26
6.03
6.02
5.97
5.15
5.14
4.33
4.19
3.73
3.14
3.13
3.11
3.10
2.45
2.39
2.17
2.10
1.97
1.91
1.89
1.43
1.36
1.34
1.33
0.95
0.93
1.00
0.91
0.96
2.38
2.83
1.09
2.27
1.34
3.06
1.18
3.22
3.10
3.22
f1 (ppm)
3.145


173.40
169.00
168.03
142.84
132.87
97.59
80.10
77.16
71.16
62.43
57.63
54.04
52.07
48.48
39.33
36.04
21.10
15.24
14.13
12.46
f1 (ppm)
3.145


7.26
5.98
5.97
4.55
4.54
4.53
4.53
4.45
4.44
4.32
4.30
4.28
4.27
3.74
3.74
2.87
2.86
2.83
2.83
2.45
2.39
2.33
2.24
2.12
2.11
2.09
2.08
1.69
1.35
1.34
1.32
0.99
0.97
0.93
0.98
0.91
2.14
1.00
3.00
1.22
1.05
1.04
2.21
1.25
3.06
3.41
3.14
f1 (ppm)
3.146


176.92
170.01
142.06
134.89
77.16
73.79
71.07
62.66
56.14
52.09
50.57
45.99
38.82
35.51
26.54
16.55
14.37
13.98
f1 (ppm)
3.146


7.26
5.73
5.72
4.57
4.56
4.55
4.19
4.04
3.79
3.77
3.69
3.47
3.45
3.04
3.02
3.00
2.99
2.84
2.83
2.36
2.25
2.12
2.04
1.72
1.69
1.35
1.25
1.23
1.22
0.91
0.90
0.93
0.96
2.02
0.97
3.00
1.02
1.04
0.99
2.14
1.12
1.07
3.24
3.05
3.24
f1 (ppm)

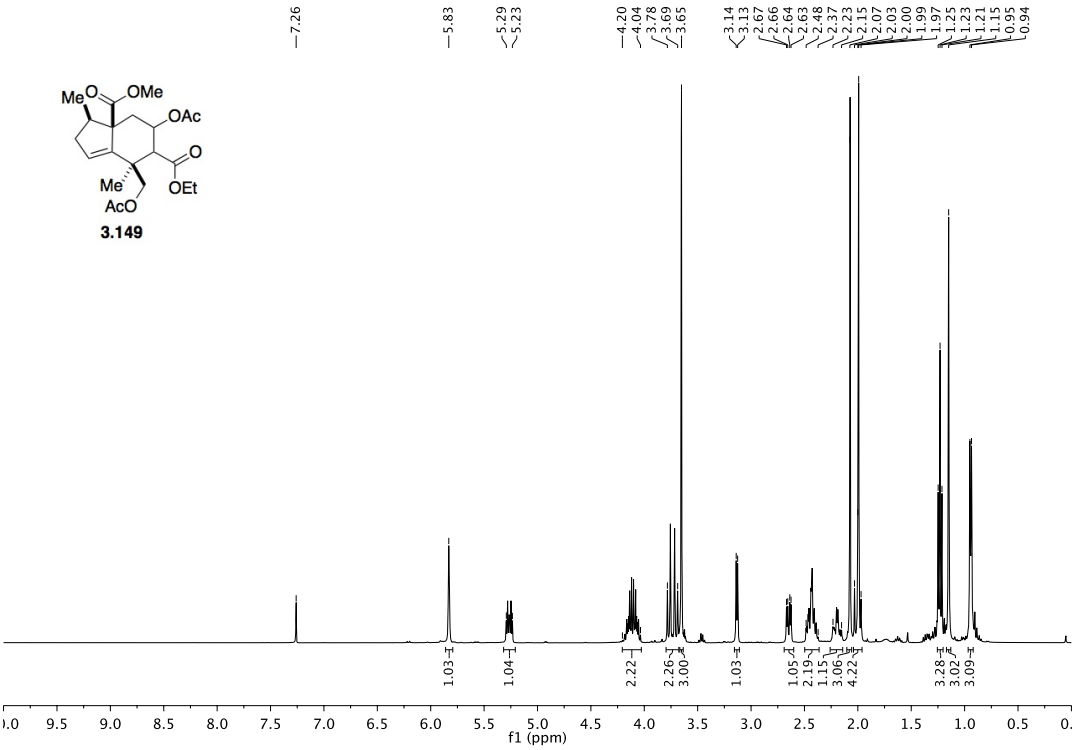

174.30
169.66
145.76
126.60
77.45
77.16
76.66
60.35
58.31
55.74
51.69
48.87
44.76
39.03
37.74
17.37
15.19
14.42
f1 (ppm)

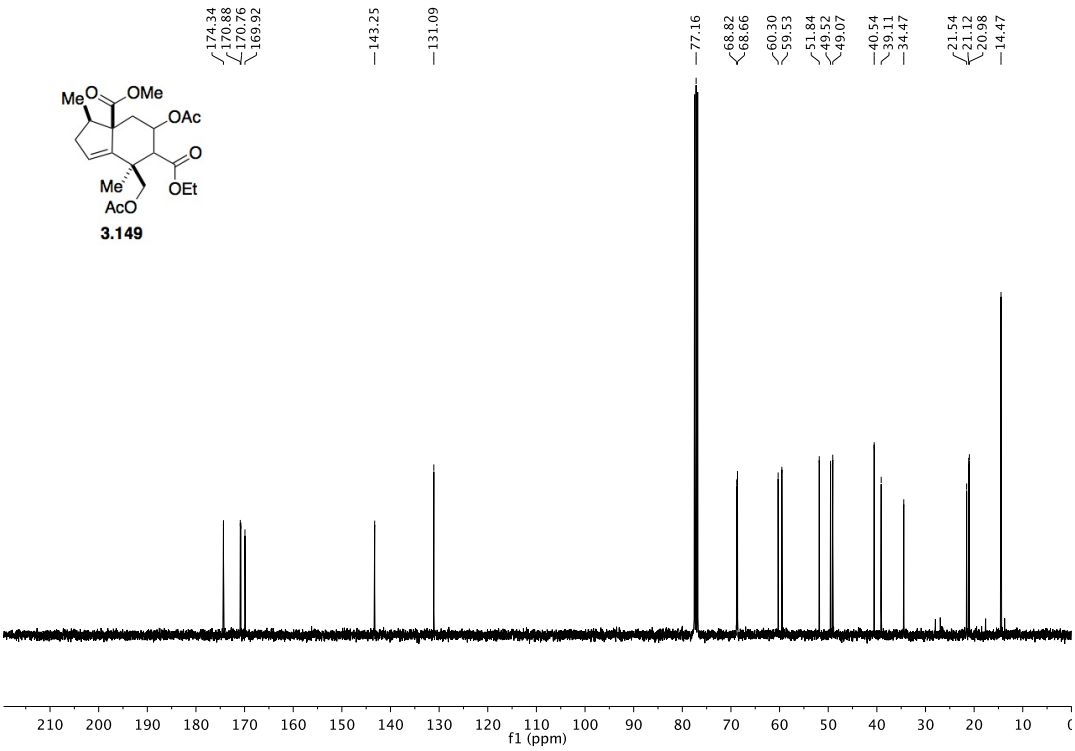
Me
O
OMe
O
O
Me
OEt

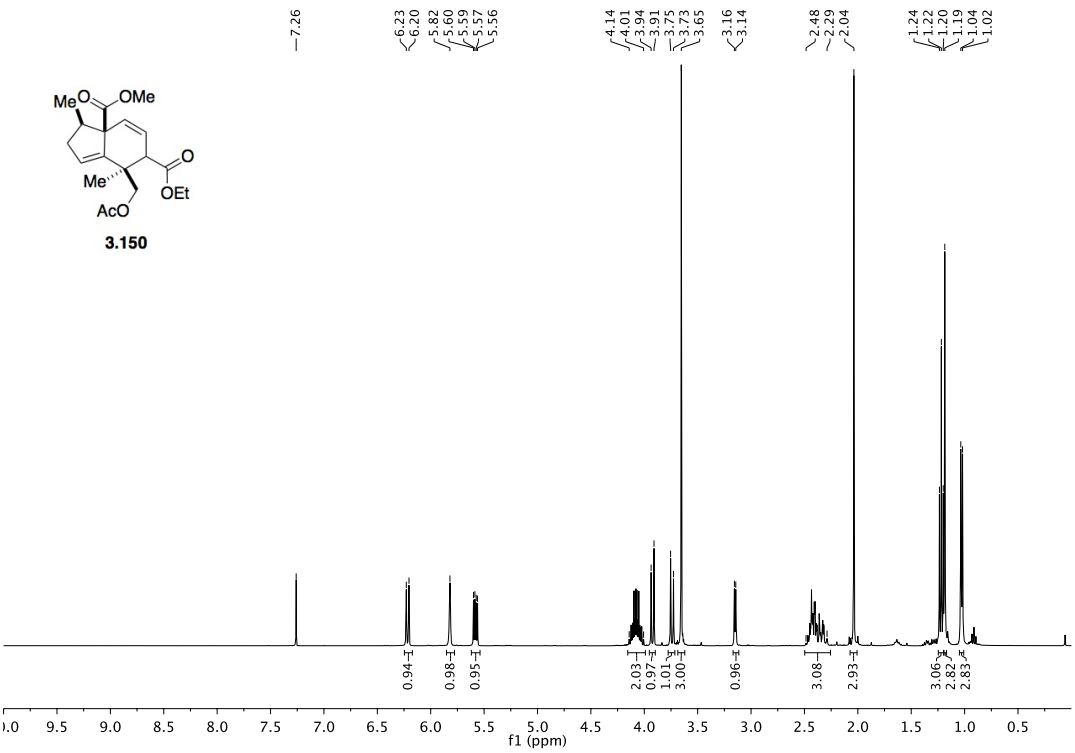
3.148

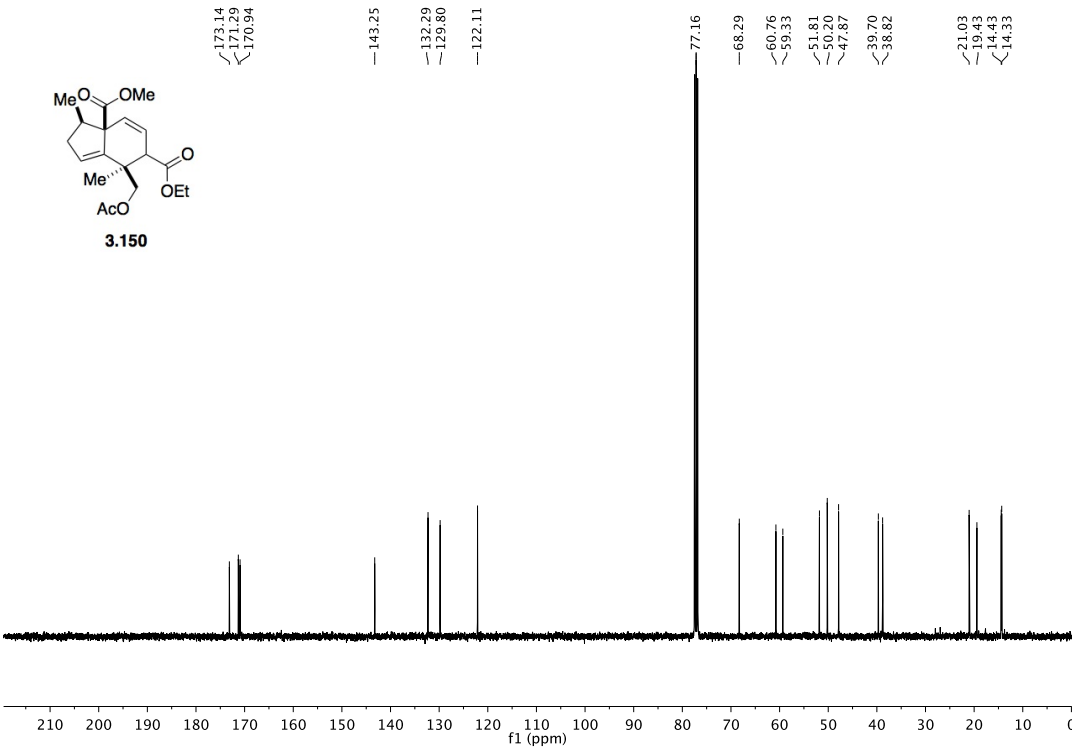
Me
O
OMe
O
O
Me
OEt

3.148


7.26
5.83
5.29
5.23
4.20
4.04
3.78
3.69
3.65
3.14
3.13
2.67
2.66
2.64
2.63
2.48
2.37
2.23
2.15
2.07
2.03
2.00
1.99
1.97
1.25
1.23
1.21
1.15
0.95
0.94
1.03
1.04
2.22
2.26
3.00
1.03
1.05
2.19
1.15
3.06
4.22
3.28
3.02
3.09
f1 (ppm)
Me
O
OMe
OAc
O
OEt
Me
AcO
3.149


174.34
170.88
170.76
169.92
143.25
131.09
77.16
68.82
68.66
60.30
59.53
51.84
49.52
49.07
40.54
39.11
34.47
21.54
21.12
20.98
14.47
f1 (ppm)
Me
O
OMe
OAc
O
OEt
Me
AcO
3.149


7.26
6.23
6.20
5.82
5.60
5.59
5.57
5.56
4.14
4.01
3.94
3.91
3.75
3.73
3.65
3.16
3.14
2.48
2.29
2.04
1.24
1.22
1.20
1.19
1.04
1.02
0.94
0.98
0.95
2.03
0.97
1.01
3.00
0.96
3.08
2.93
3.06
2.82
2.83
f1 (ppm)

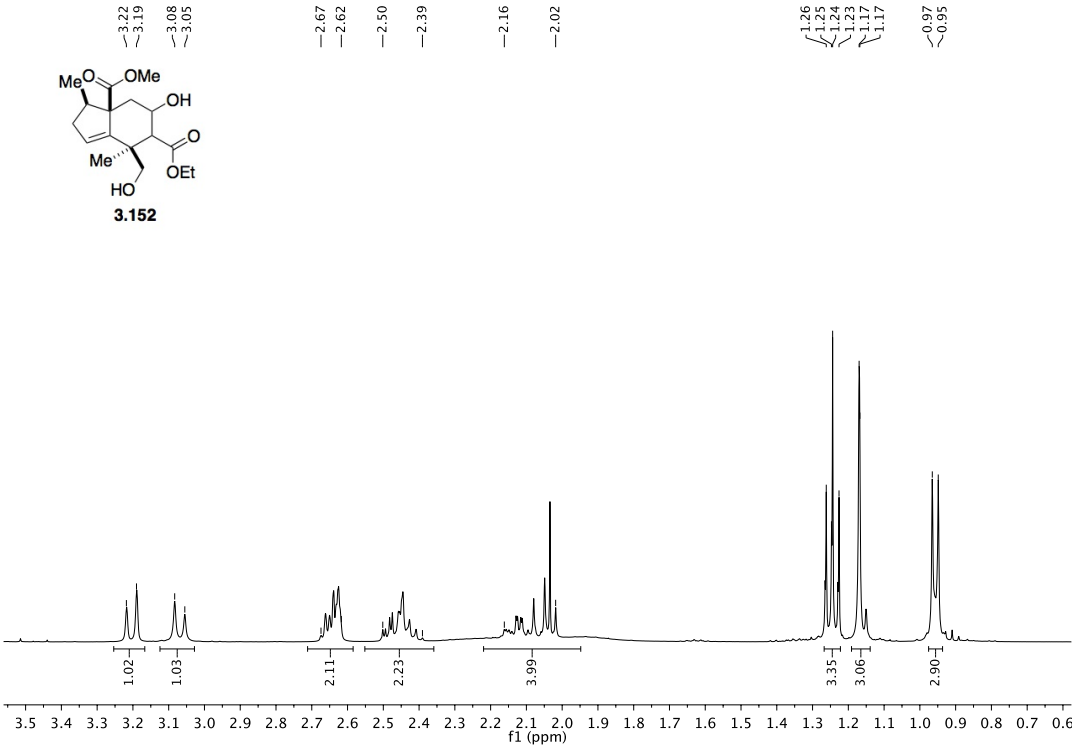

173.14
171.29
170.94
143.25
132.29
129.80
122.11
77.16
68.29
60.76
59.33
51.81
50.20
47.87
39.70
38.82
21.03
19.43
14.43
14.33
f1 (ppm)

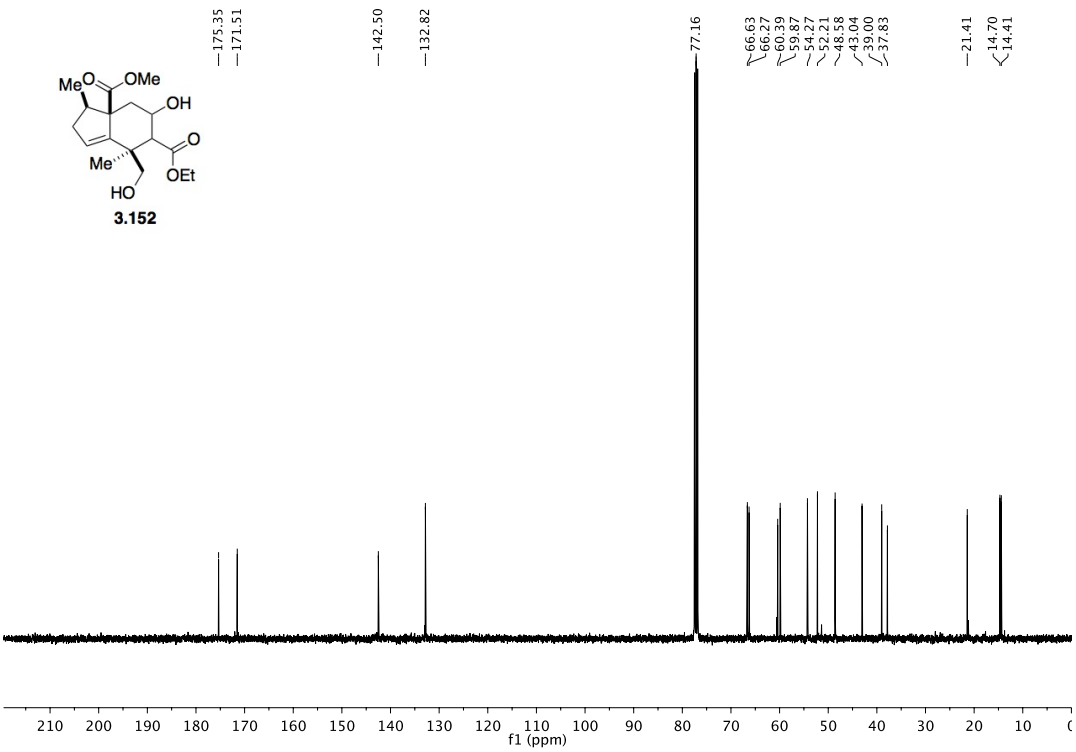
Me
O
OMe
O
Me
OEt
AcO

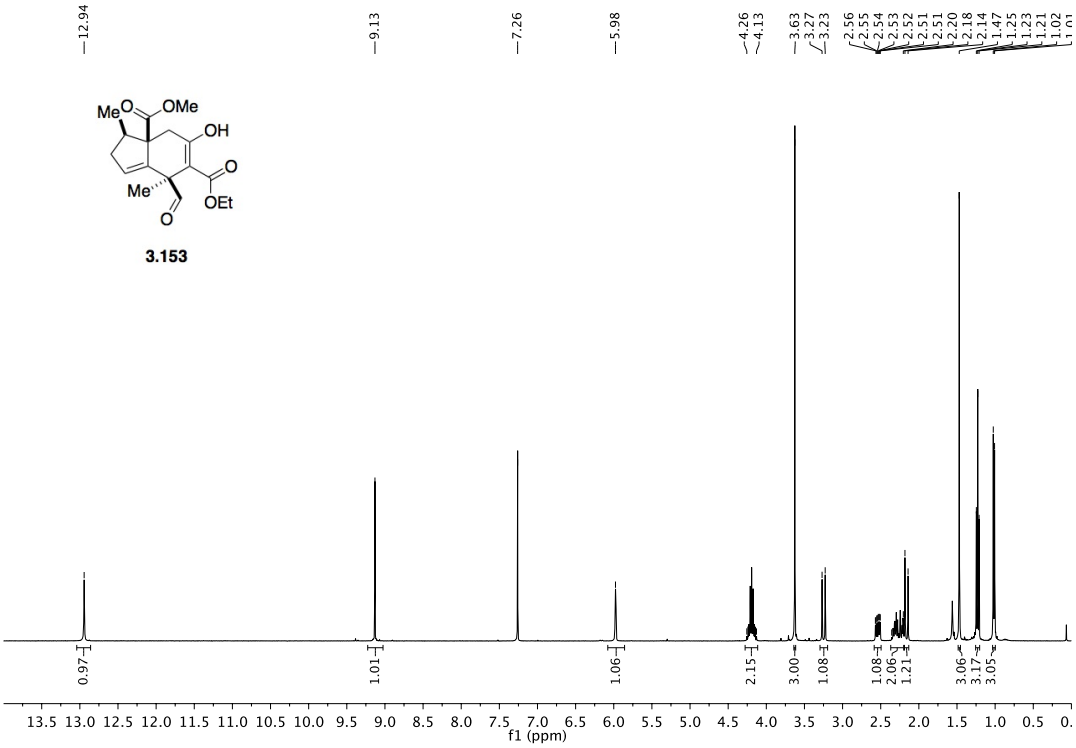
3.150

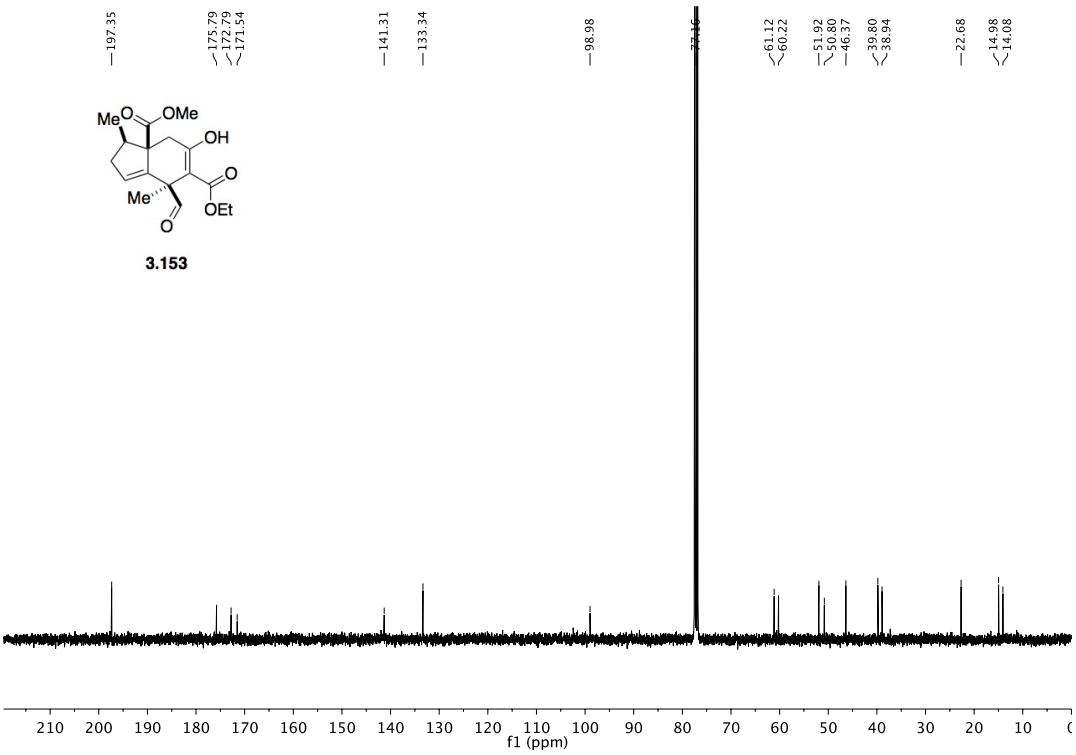
Me
O
OMe
O
Me
OEt
AcO

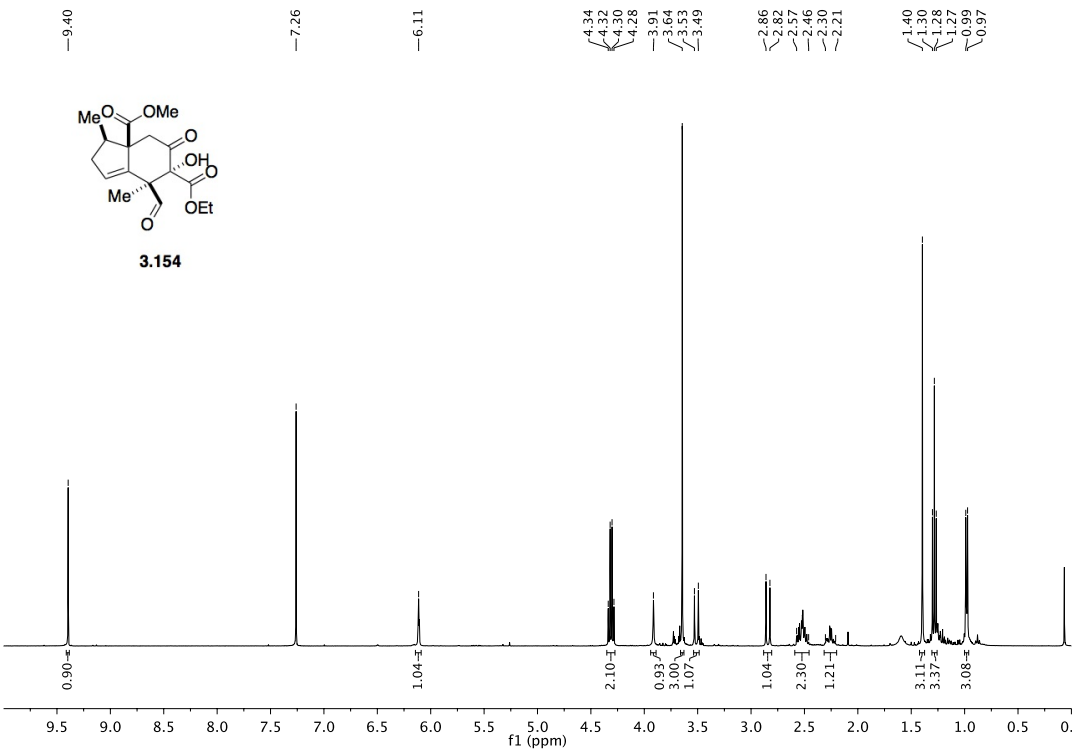
3.150

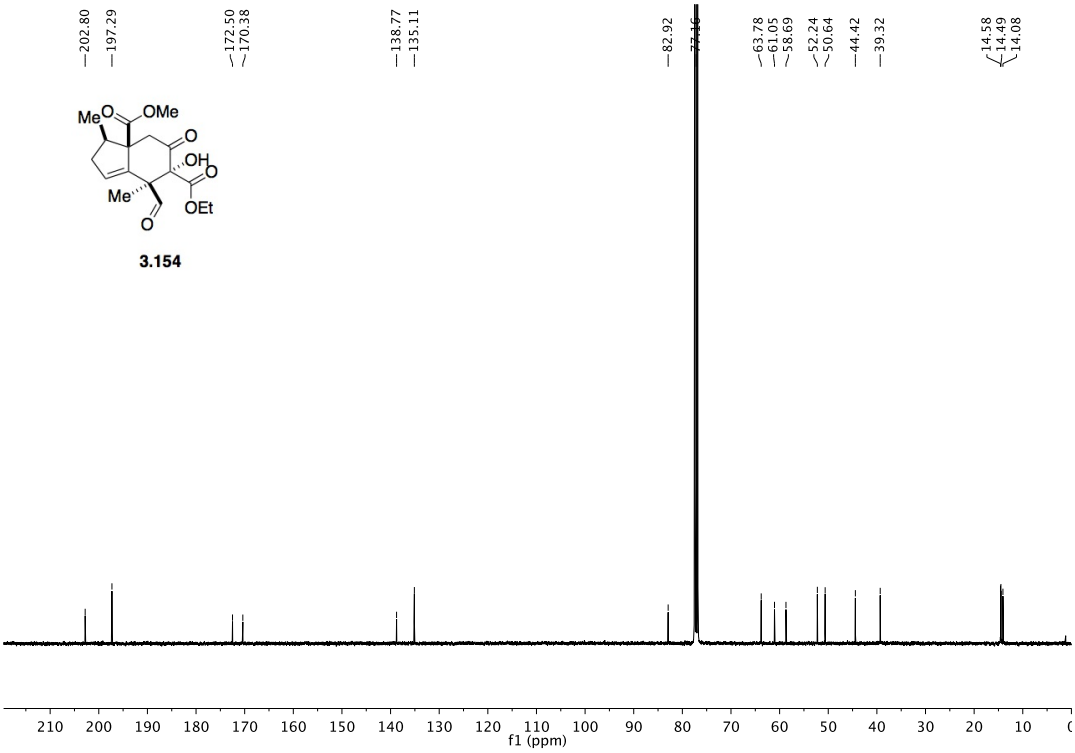

3.22
3.19
3.08
3.05
2.67
2.62
2.50
2.39
2.16
2.02
1.26
1.25
1.24
1.23
1.17
1.17
0.97
0.95
Me
O
OMe
OH
O
OEt
Me
HO
3.152
1.02
1.03
2.11
2.23
3.99
3.35
3.06
2.90
f1 (ppm)

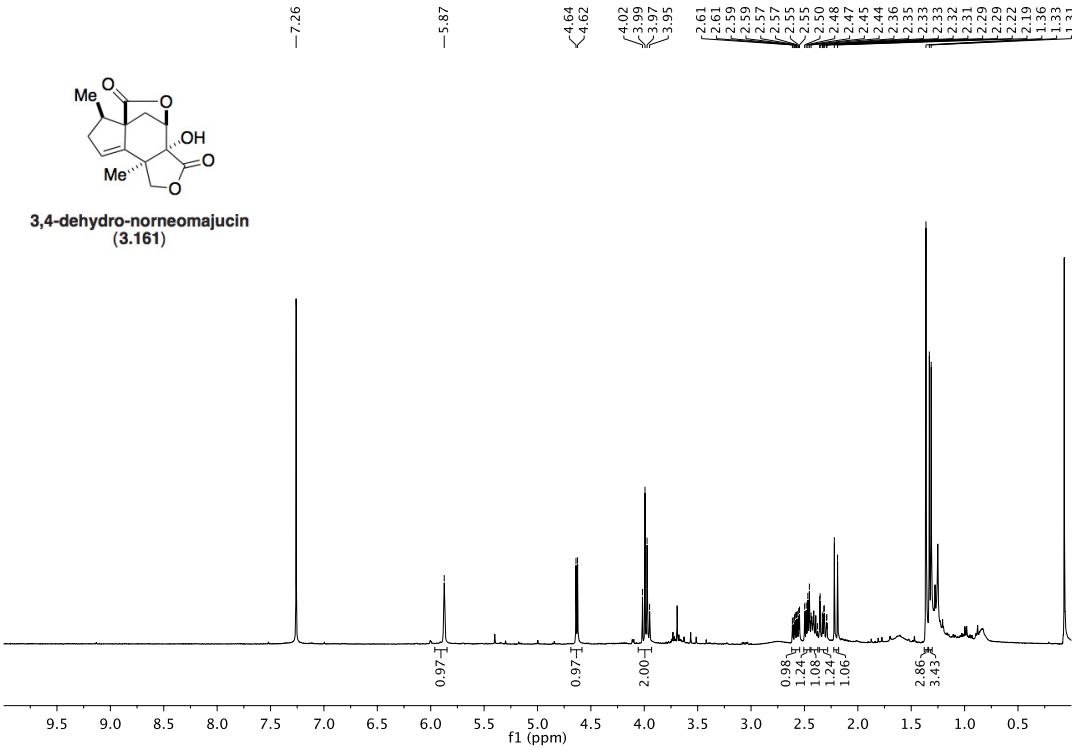

175.35
171.51
142.50
132.82
77.16
66.63
66.27
60.39
59.87
54.27
52.21
48.58
43.04
39.00
37.83
21.41
14.70
14.41
Me
O
OMe
OH
O
OEt
Me
HO
3.152
f1 (ppm)

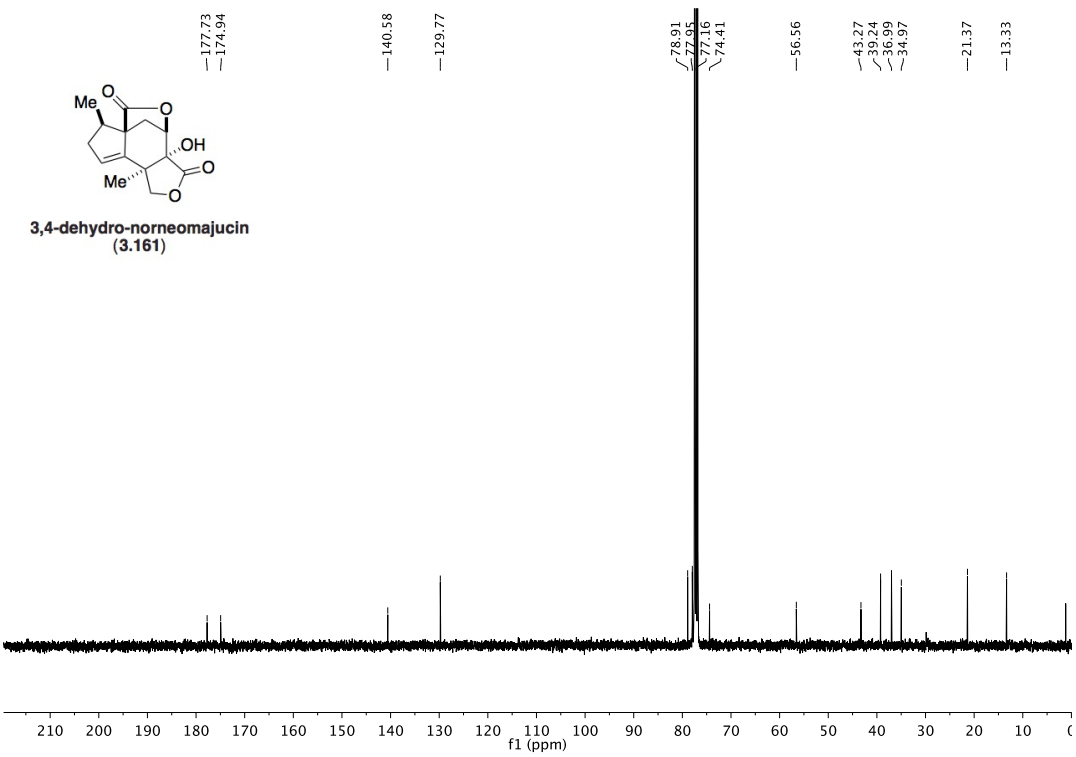

12.94
9.13
7.26
5.98
4.26
4.13
3.63
3.27
3.23
2.56
2.55
2.54
2.53
2.52
2.51
2.51
2.20
2.18
2.14
1.47
1.25
1.23
1.21
1.02
Me
O
OMe
OH
O
Me
OEt
O
3.153
0.97
1.01
1.06
2.15
3.00
1.08
1.08
2.06
1.21
3.06
3.17
3.05
13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

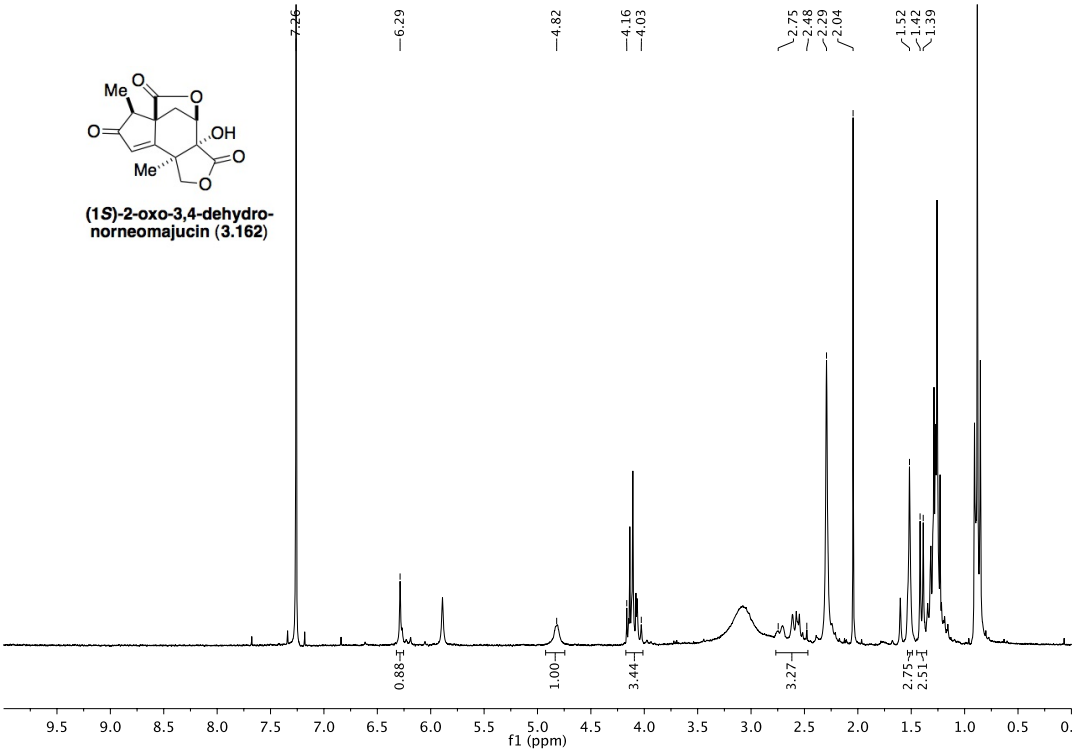

197.35
175.79
172.79
171.54
141.31
133.34
98.98
77.16
61.12
60.22
51.92
50.80
46.37
39.80
38.94
22.68
14.98
14.08
Me
O
OMe
OH
O
Me
OEt
O
3.153
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

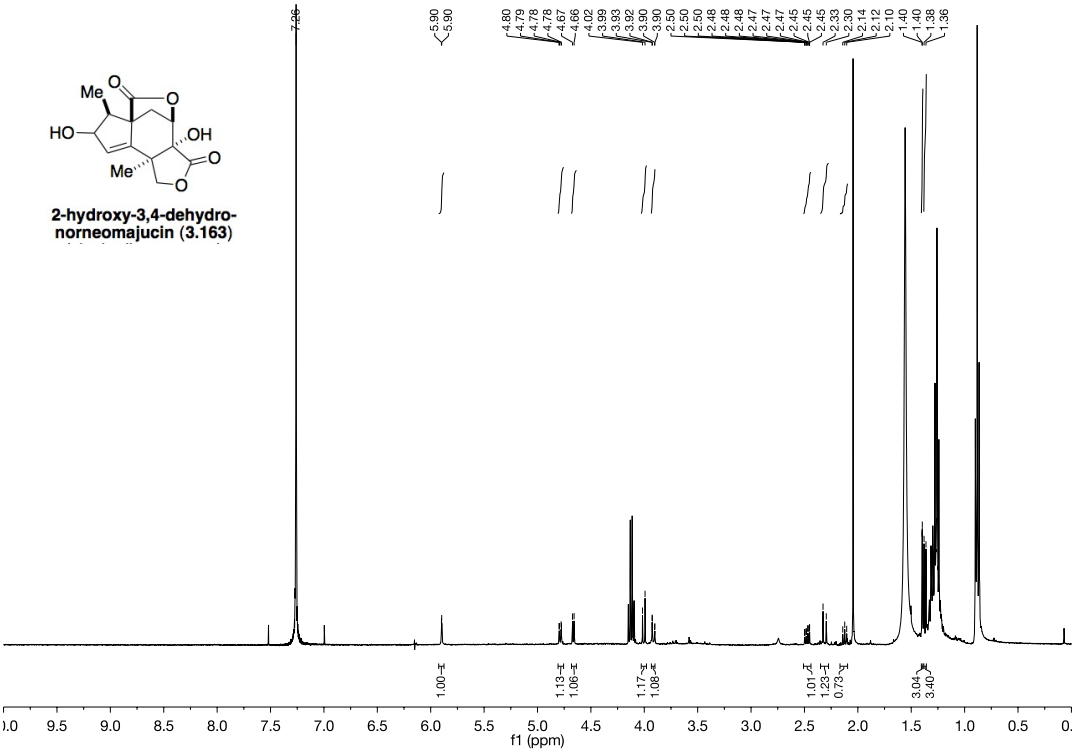

9.40
7.26
6.11
4.34
4.32
4.30
4.28
3.91
3.64
3.53
3.49
2.86
2.82
2.57
2.46
2.30
2.21
1.40
1.30
1.28
1.27
0.99
0.97
Me
O
OMe
O
OH
O
Me
OEt
O
3.154
0.90
1.04
2.10
0.93
3.00
1.07
1.04
2.30
1.21
3.11
3.37
3.08
f1 (ppm)

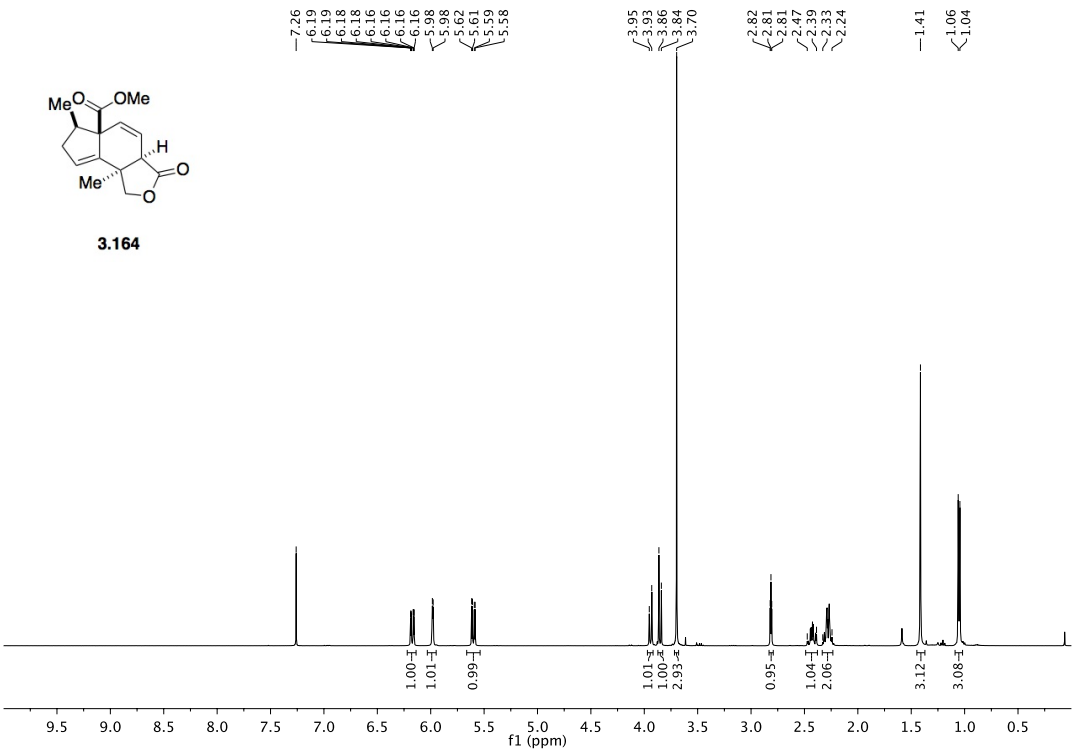

202.80
197.29
172.50
170.38
138.77
135.11
82.92
77.16
63.78
61.05
58.69
52.24
50.64
44.42
39.32
14.58
14.49
14.08
Me
O
OMe
O
OH
O
Me
OEt
O
3.154
f1 (ppm)


7.26
5.87
4.64
4.62
4.02
3.99
3.97
3.95
2.61
2.61
2.59
2.59
2.57
2.57
2.55
2.55
2.50
2.48
2.47
2.45
2.44
2.36
2.35
2.33
2.33
2.32
2.31
2.29
2.29
2.22
2.19
1.36
1.33
Me
O
O
OH
O
Me
O
3,4-dehydro-norneomajucin
(3.161)
0.97
0.97
2.00
0.98
1.24
1.08
1.24
1.06
2.86
3.43
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

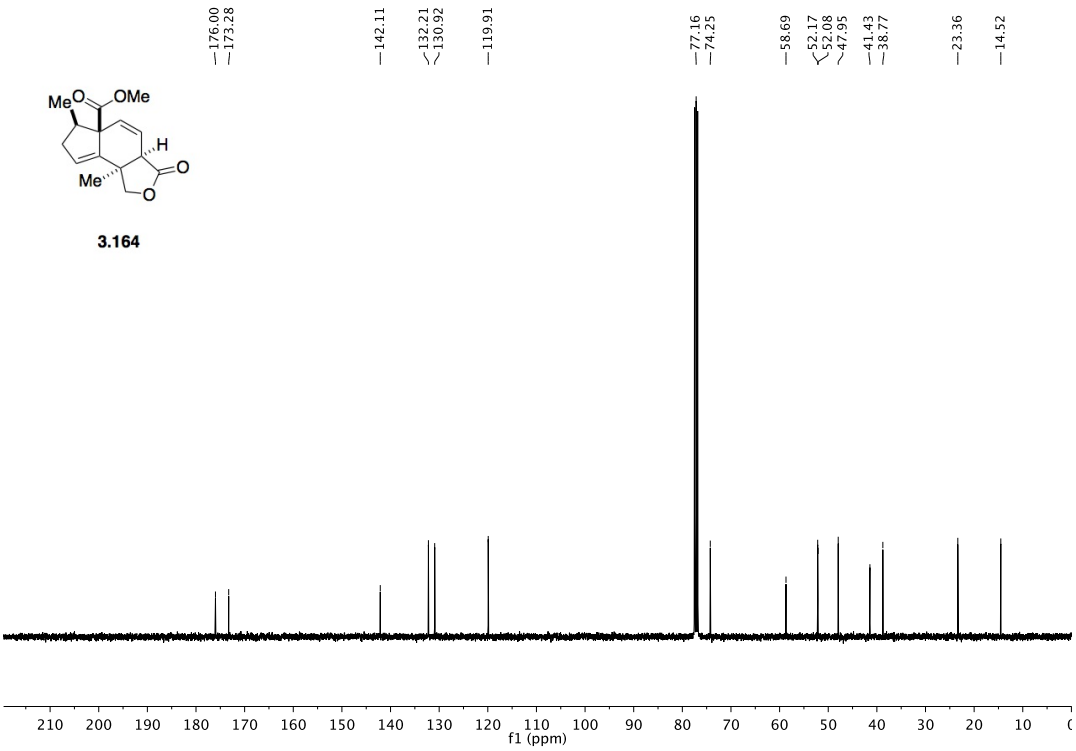

177.73
174.94
140.58
129.77
78.91
77.95
77.16
74.41
56.56
43.27
39.24
36.99
34.97
21.37
13.33
Me
O
O
OH
O
Me
O
3,4-dehydro-norneomajucin
(3.161)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


(1S)-2-oxo-3,4-dehydro-
norneomajucin (3.162)
f1 (ppm)

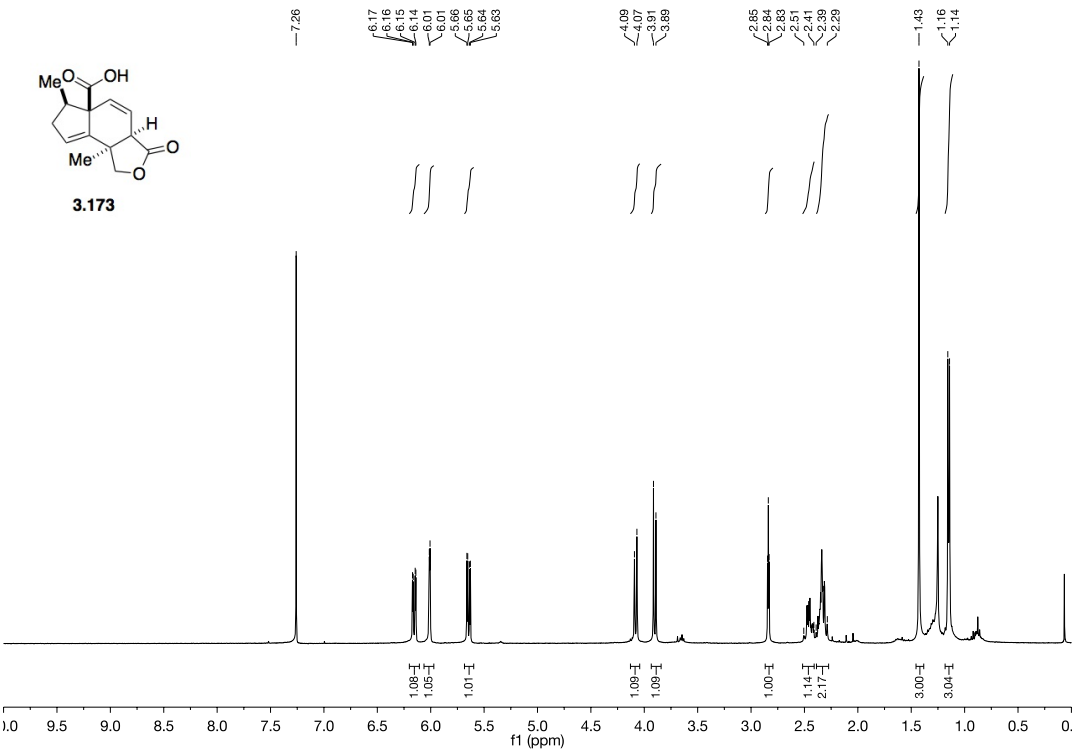

2-hydroxy-3,4-dehydro-
norneomajucin (3.163)
f1 (ppm)

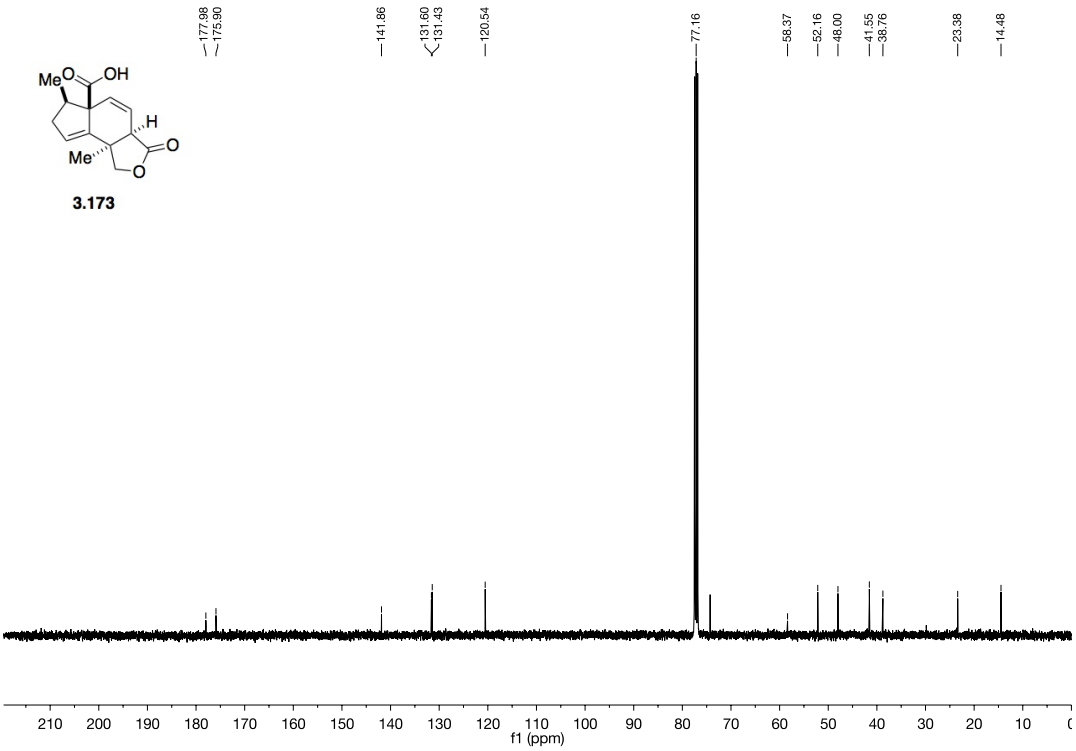

7.26
6.19
6.19
6.18
6.18
6.16
6.16
6.16
6.16
5.98
5.98
5.62
5.61
5.59
5.58
3.95
3.93
3.86
3.84
3.70
2.82
2.81
2.81
2.47
2.39
2.33
2.24
1.41
1.06
1.04
Me
O
OMe
H
O
Me
O
1.00
1.01
0.99
1.01
1.00
2.93
0.95
1.04
2.06
3.12
3.08
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

3.164

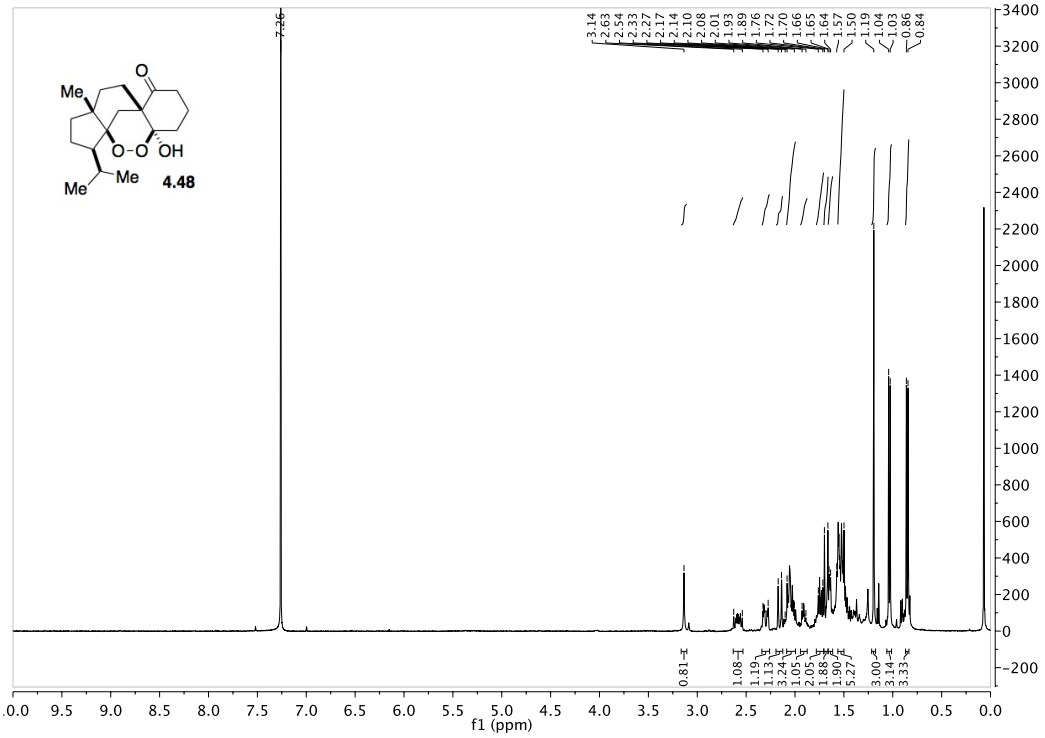

176.00
173.28
142.11
132.21
130.92
119.91
77.16
74.25
58.69
52.17
52.08
47.95
41.43
38.77
23.36
14.52
Me
O
OMe
H
O
Me
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

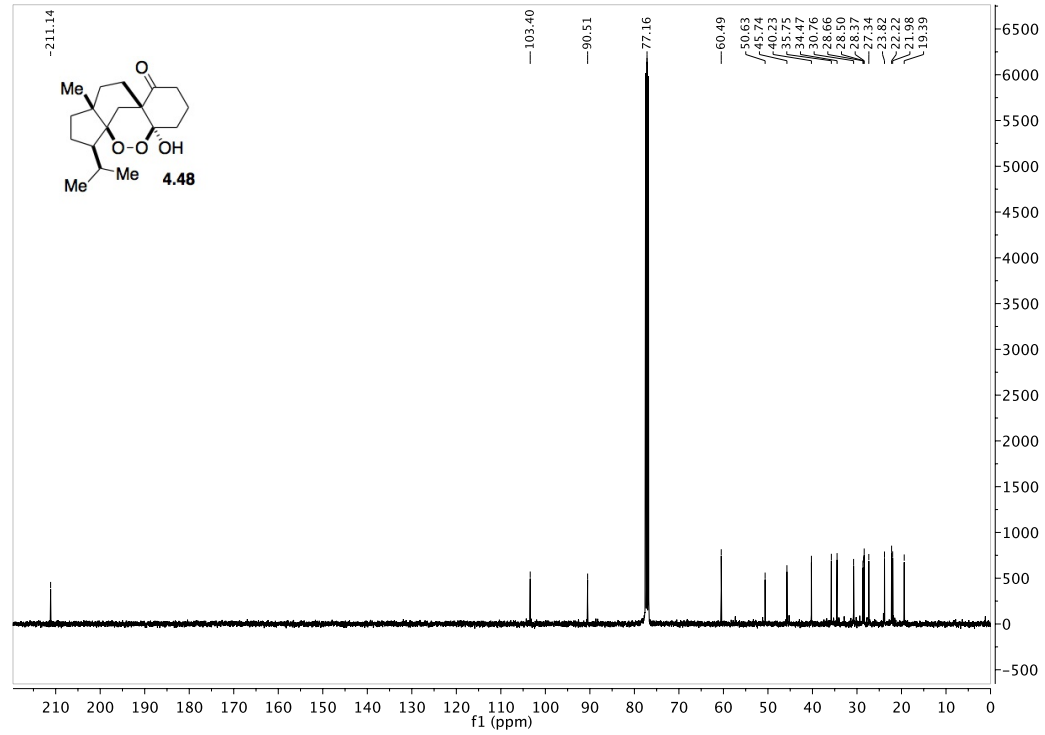
3.164

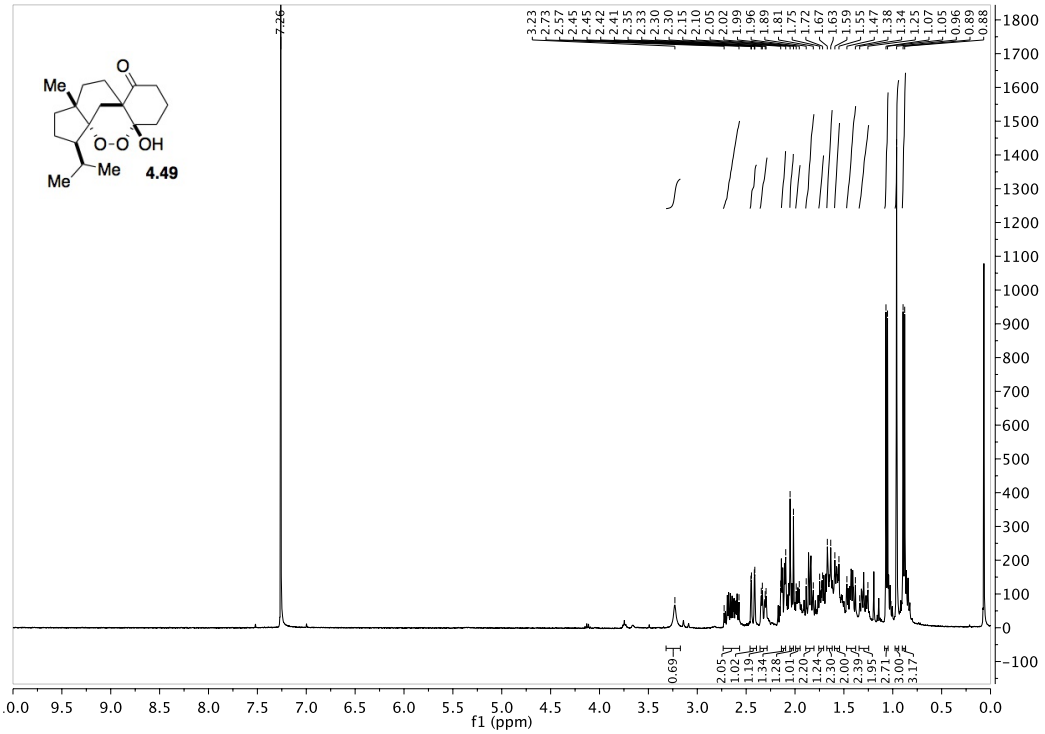

7.26
6.17
6.16
6.15
6.14
6.01
6.01
5.66
5.65
5.64
5.63
4.09
4.07
3.91
3.89
2.85
2.84
2.83
2.41
2.39
2.29
1.43
1.16
1.14
1.08
1.05
1.01
1.09
1.09
1.00
1.14
2.17
3.00
3.04
f1 (ppm)
Me
O
OH
H
O
Me
O
3.173

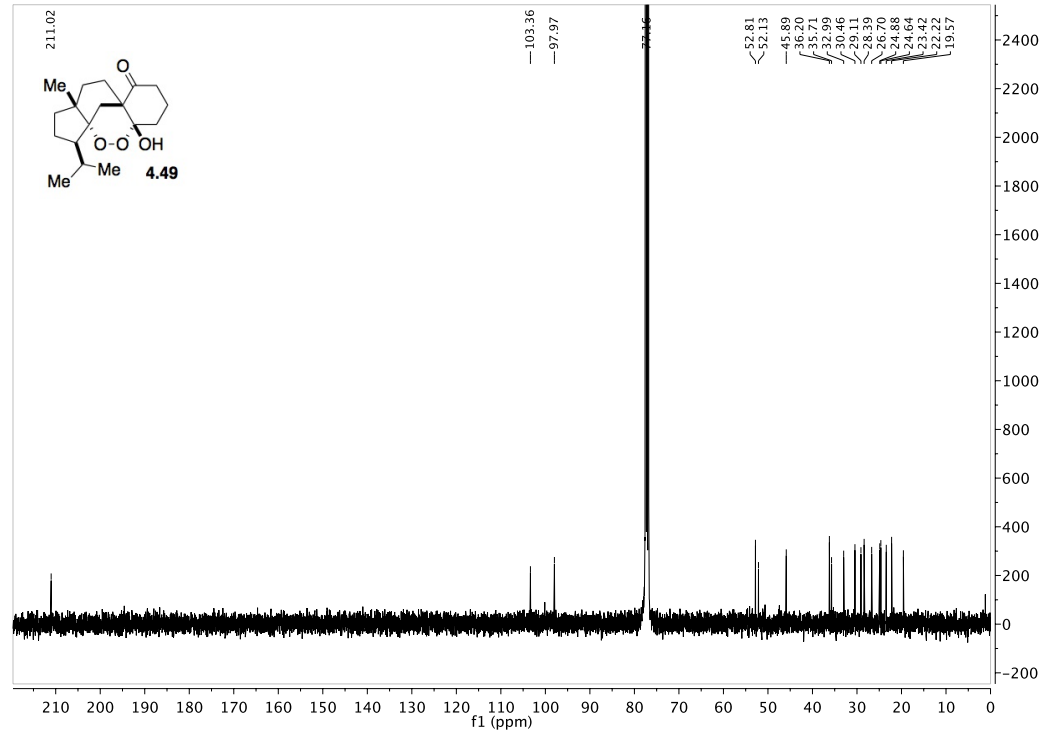

177.98
175.90
141.86
131.60
131.43
120.54
77.16
58.37
52.16
48.00
41.55
38.76
23.38
14.48
f1 (ppm)
Me
O
OH
H
O
Me
O
3.173

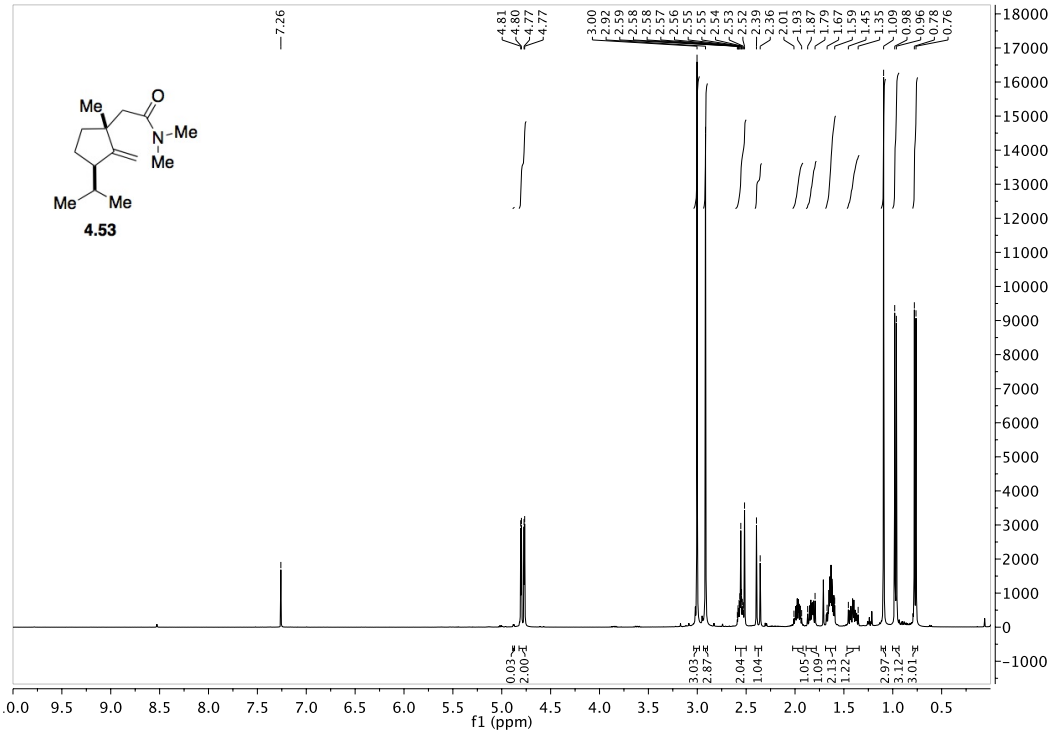
8.3.3 Preparation of Antimalarial Endoperoxides

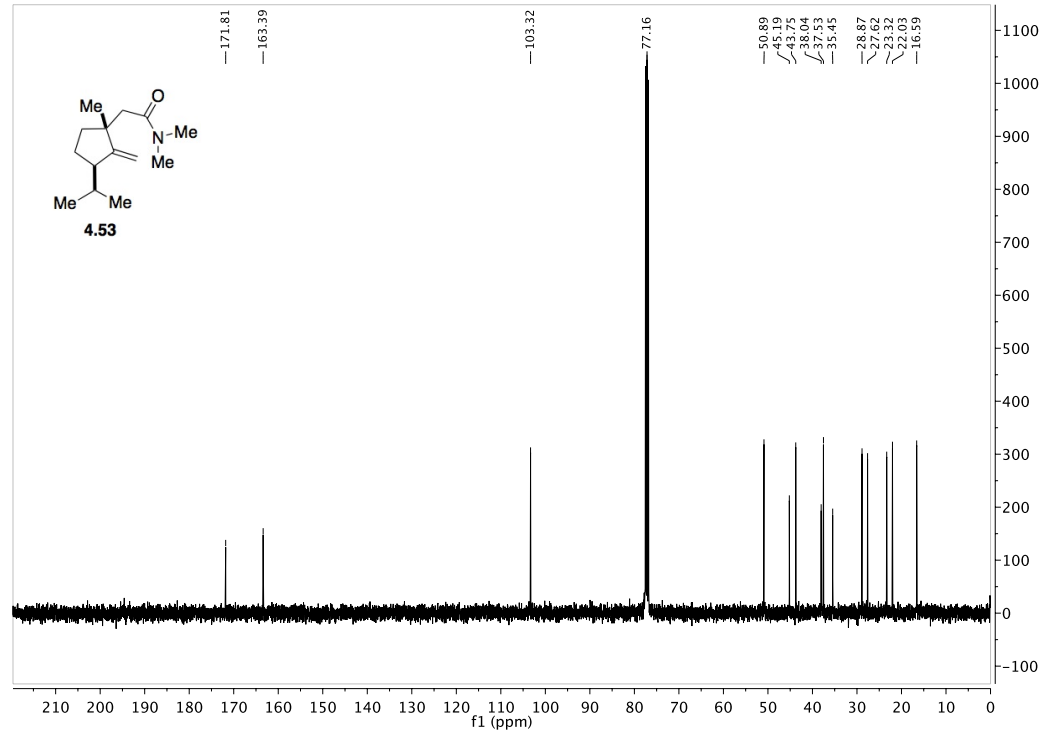


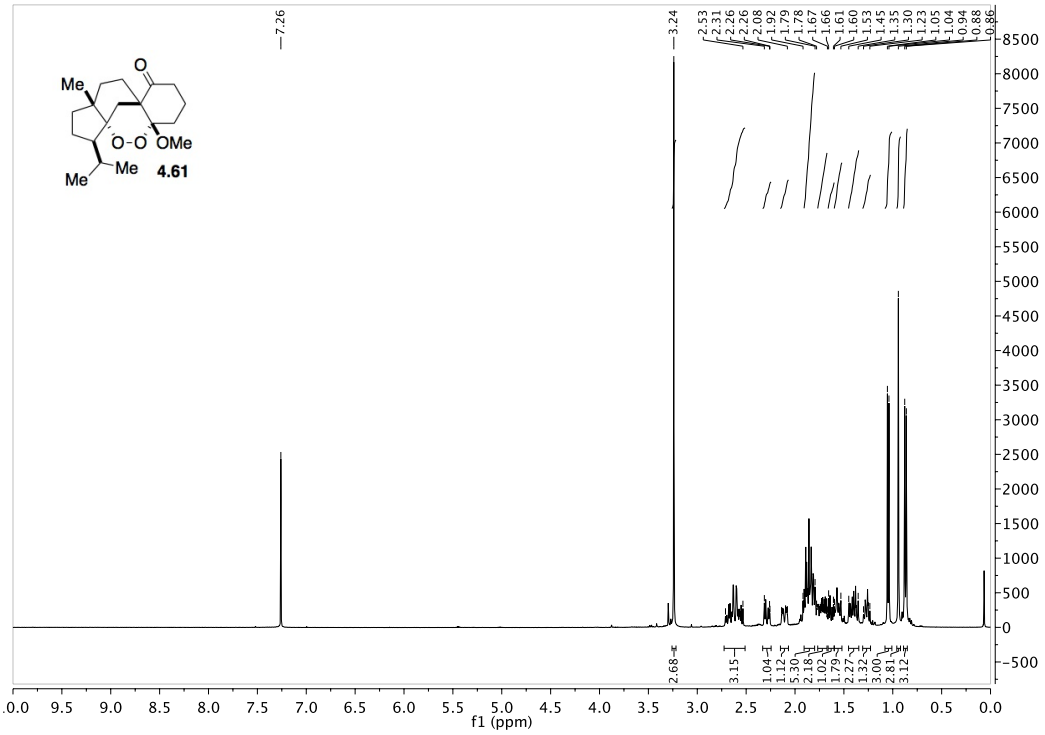


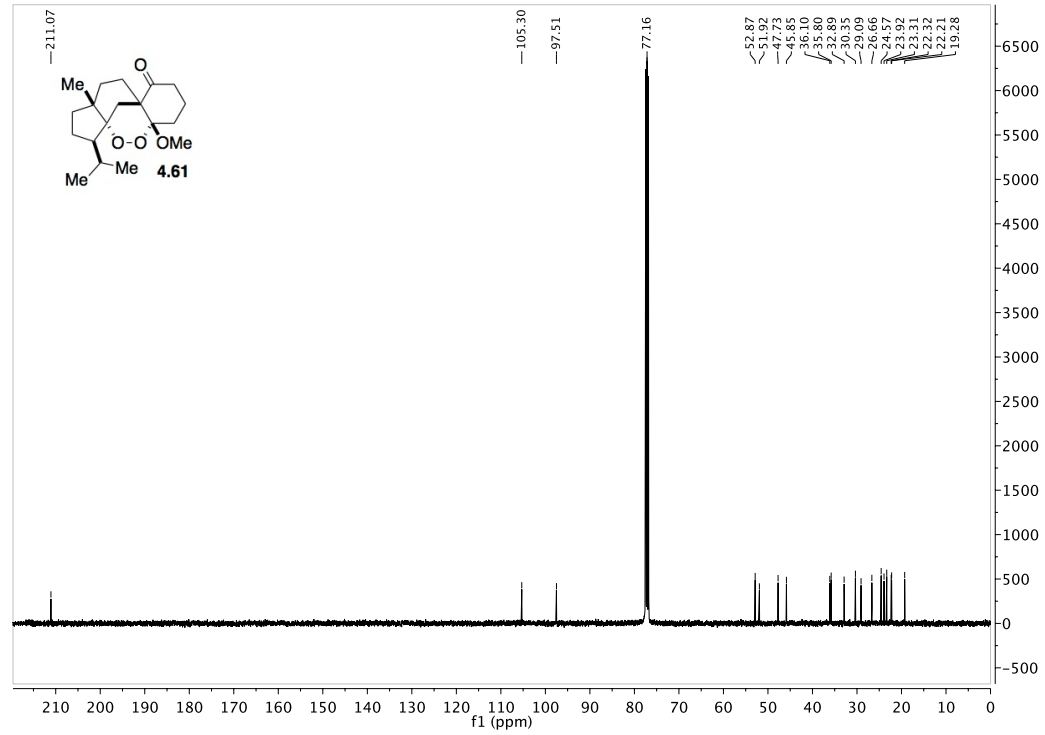

Me
O
O-O
OH
Me
Me
4.49
7.26
f1 (ppm)

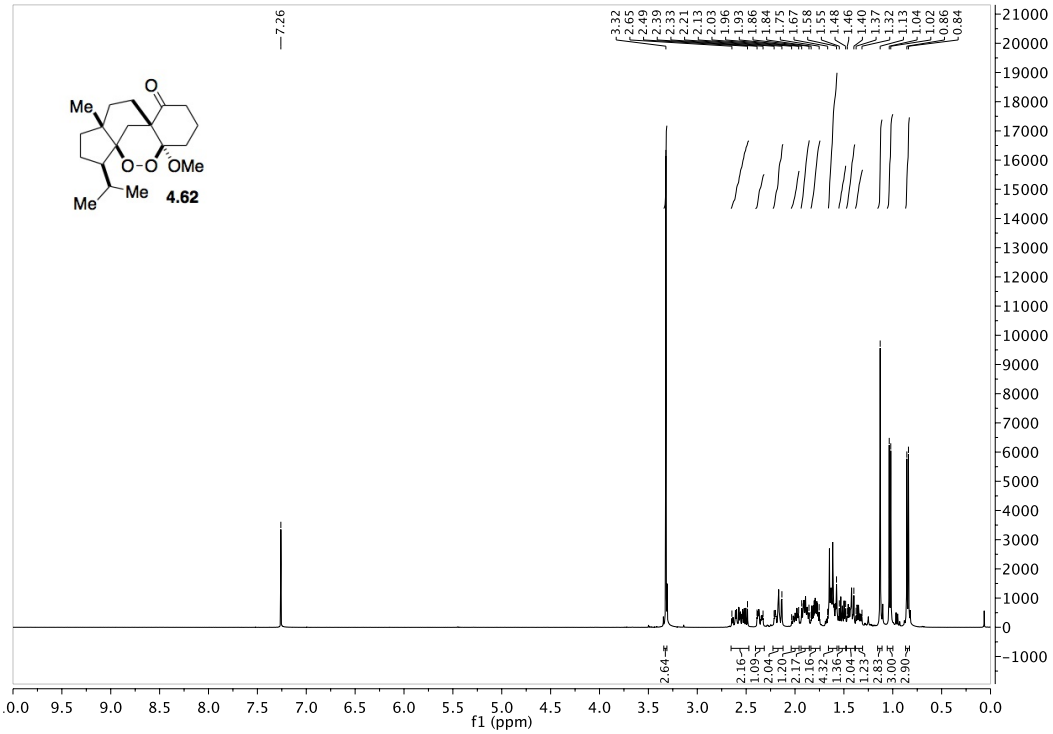

211.02
Me
O
O-O
OH
Me
Me
4.49
103.36
97.97
77.16
52.81
52.13
45.89
36.20
35.71
32.99
30.46
29.11
28.39
26.70
24.88
24.64
23.42
22.22
19.57
f1 (ppm)

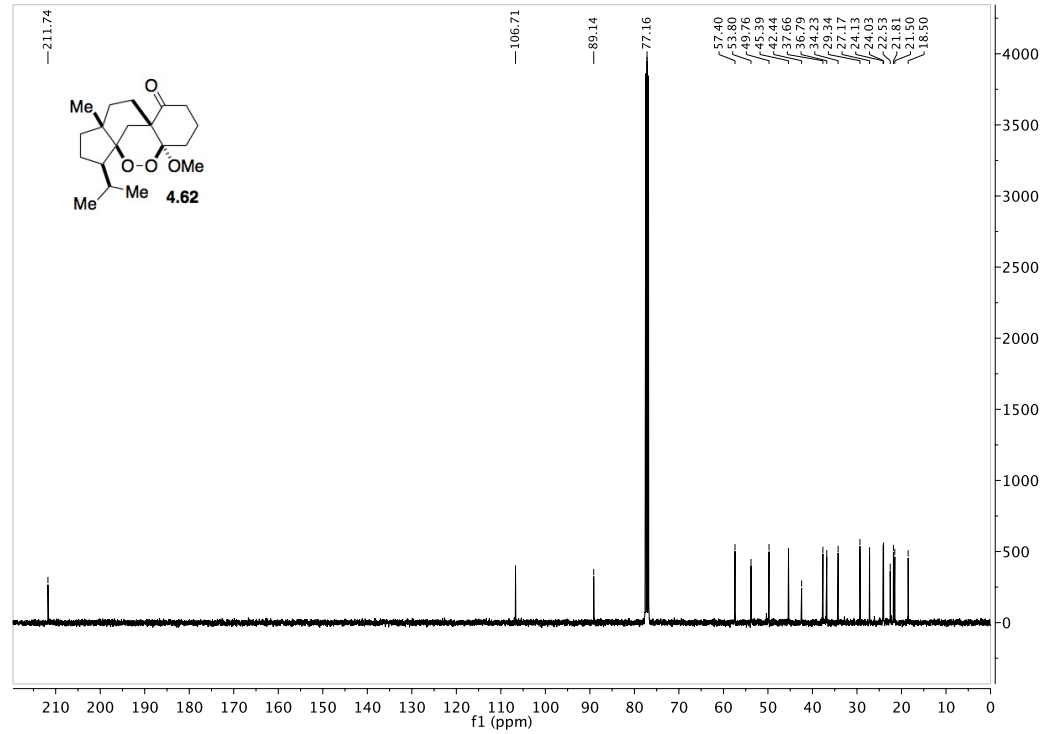

Me
O
N-Me
Me
Me
Me
4.53
7.26
4.81
4.80
4.77
4.77
3.00
2.92
2.59
2.58
2.58
2.57
2.56
2.55
2.55
2.54
2.53
2.52
2.39
2.36
2.01
1.93
1.87
1.79
1.67
1.59
1.45
1.35
1.09
1.08
0.96
0.78
0.76
0.03
2.00
3.03
2.87
2.04
1.04
1.05
1.09
2.13
1.22
2.97
3.12
3.01
f1 (ppm)

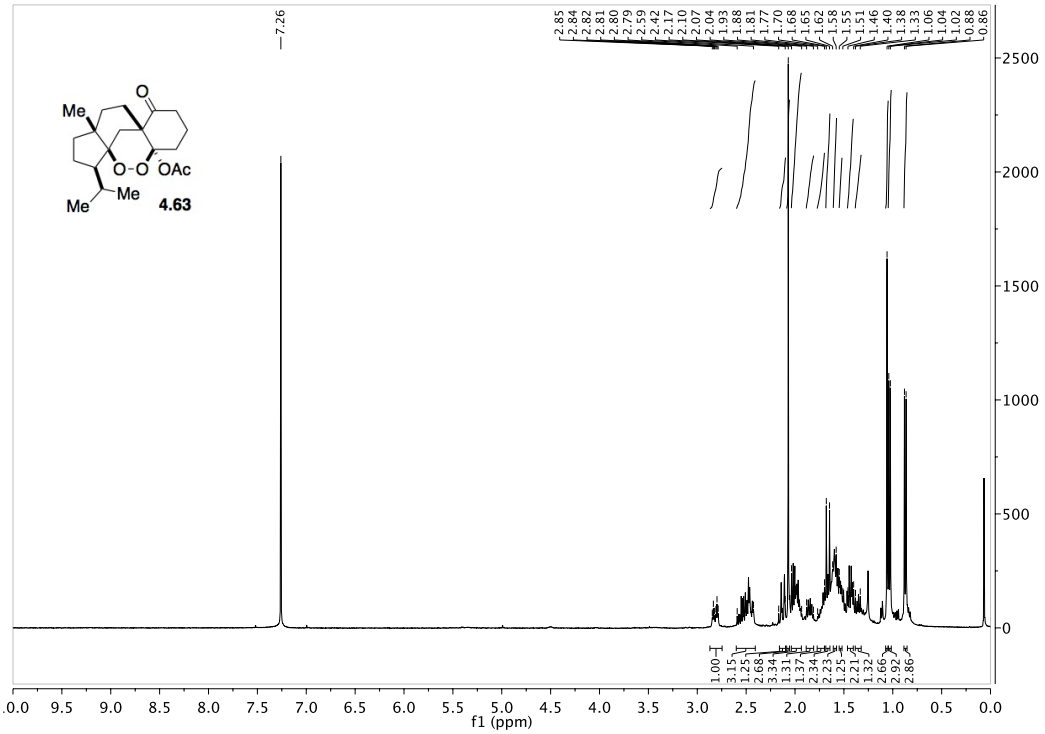

Me
O
N-Me
Me
Me
Me
4.53
171.81
163.39
103.32
77.16
50.89
45.19
43.75
38.04
37.53
35.45
28.87
27.62
23.32
22.03
16.59
f1 (ppm)

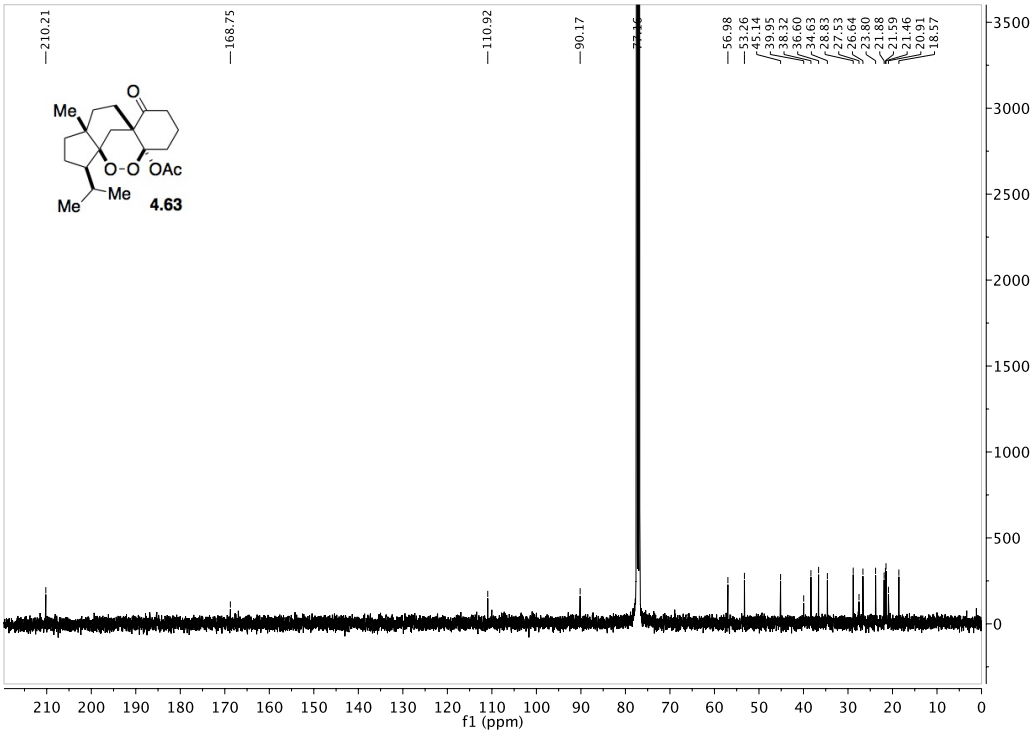

Me
O
O-O
OMe
Me
Me
4.61
7.26
3.24
2.53
2.31
2.26
2.26
2.08
1.92
1.79
1.78
1.67
1.66
1.61
1.60
1.53
1.45
1.35
1.30
1.23
1.05
1.04
0.88
0.86
2.68
3.15
1.04
1.12
5.16
2.18
1.02
1.79
2.27
1.32
3.00
2.81
3.12
f1 (ppm)


Me
O
O-O
OMe
Me
Me
4.61
211.07
105.30
97.51
77.16
52.87
51.92
47.73
45.85
36.10
35.80
32.89
30.35
29.09
26.66
24.57
23.92
23.31
22.32
22.21
19.28
f1 (ppm)

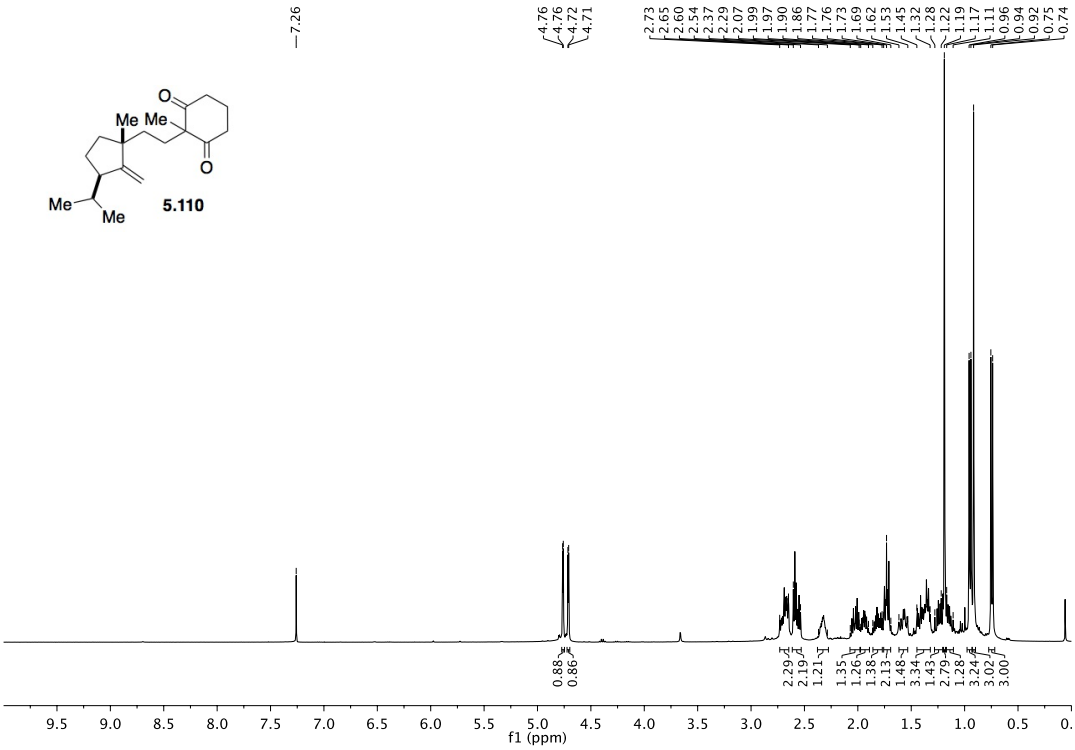

7.26
3.32
2.65
2.49
2.39
2.33
2.21
2.13
2.03
1.96
1.93
1.86
1.84
1.75
1.67
1.58
1.55
1.48
1.46
1.40
1.37
1.32
1.13
1.04
1.02
0.86
0.84
Me
O
O-O
OMe
Me
Me
4.62
2.64
2.16
1.09
2.04
1.20
2.17
2.16
4.32
1.06
1.04
1.23
2.83
3.00
2.90
f1 (ppm)

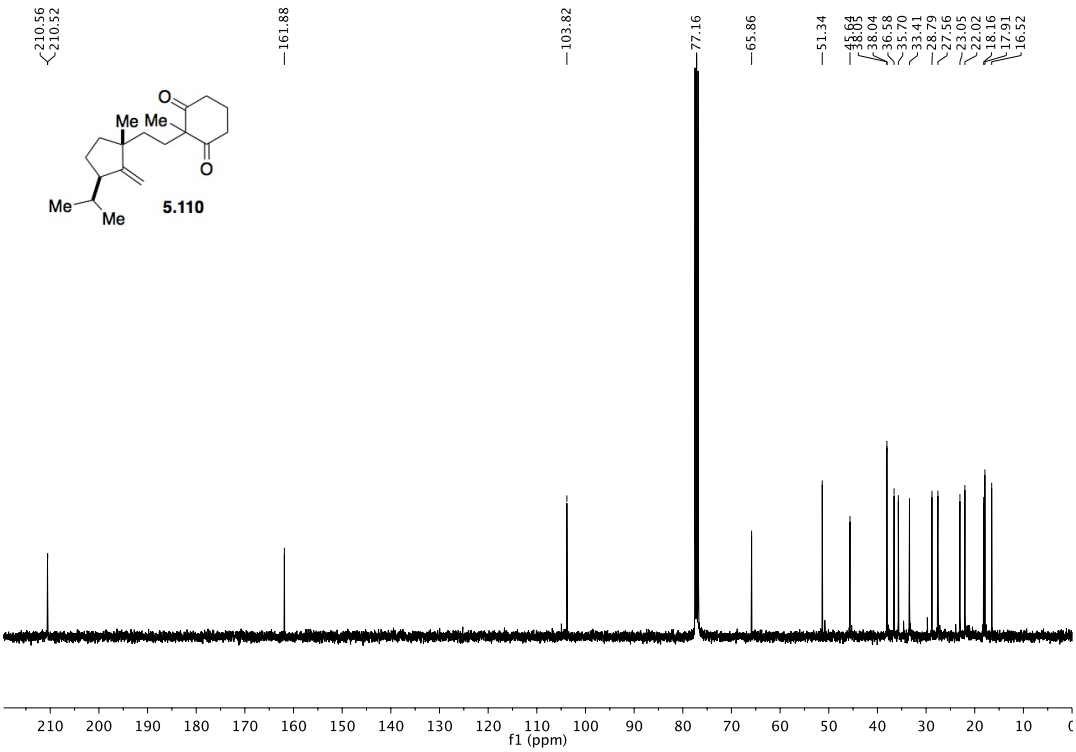

211.74
106.71
89.14
77.16
57.40
53.80
49.76
45.39
42.44
37.66
36.79
34.23
29.34
27.17
24.13
24.03
22.53
21.81
21.50
18.50
Me
O
O-O
OMe
Me
Me
4.62
f1 (ppm)

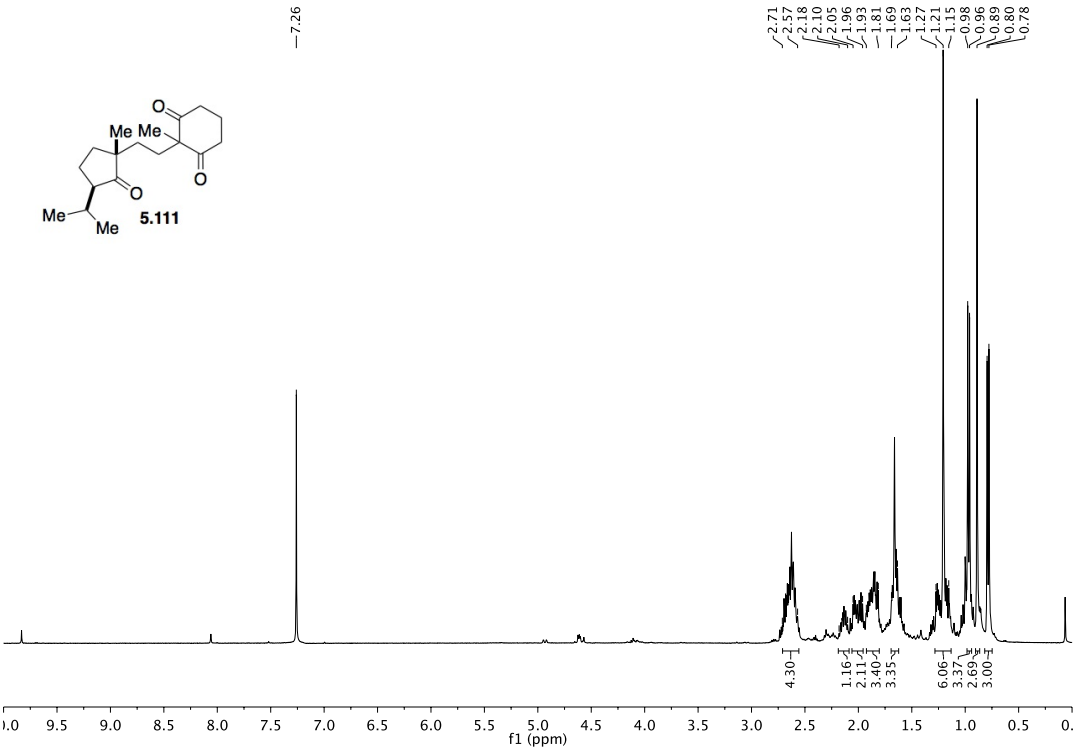

7.26
Me
O
O-O
OAc
Me
Me
4.63
f1 (ppm)

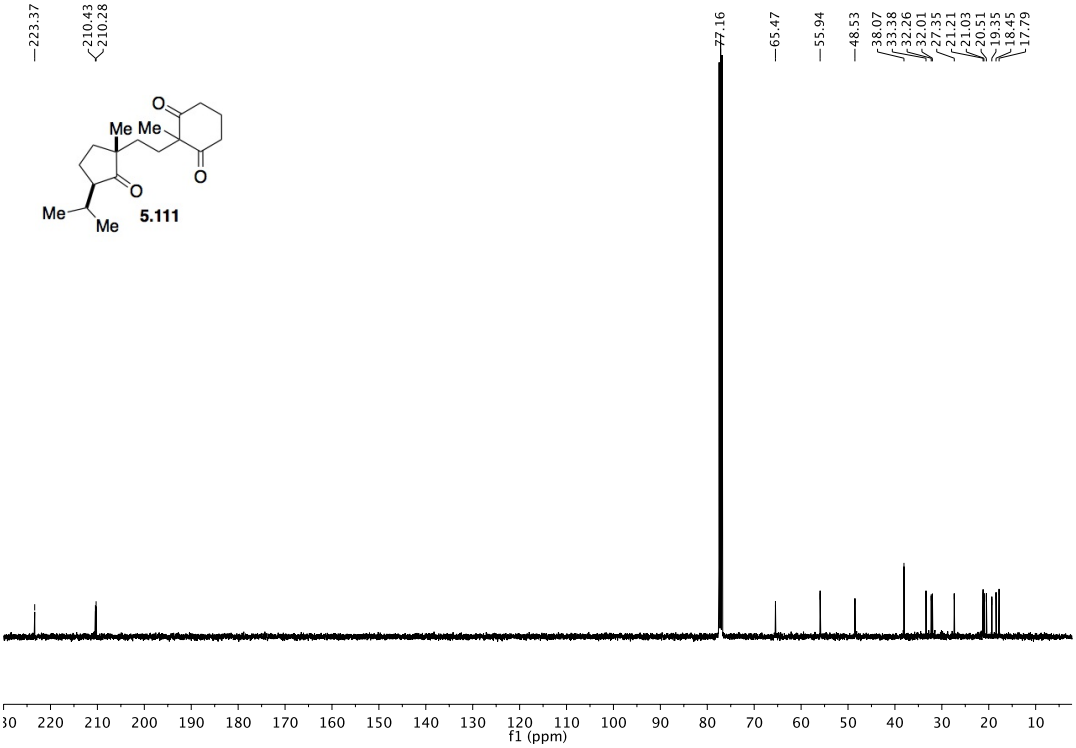

210.21
168.75
110.92
90.17
77.16
56.98
53.26
45.14
39.95
38.32
36.60
34.63
28.83
27.53
26.64
23.80
21.88
21.59
21.46
20.91
18.57
Me
O
O-O
OAc
Me
Me
4.63
f1 (ppm)

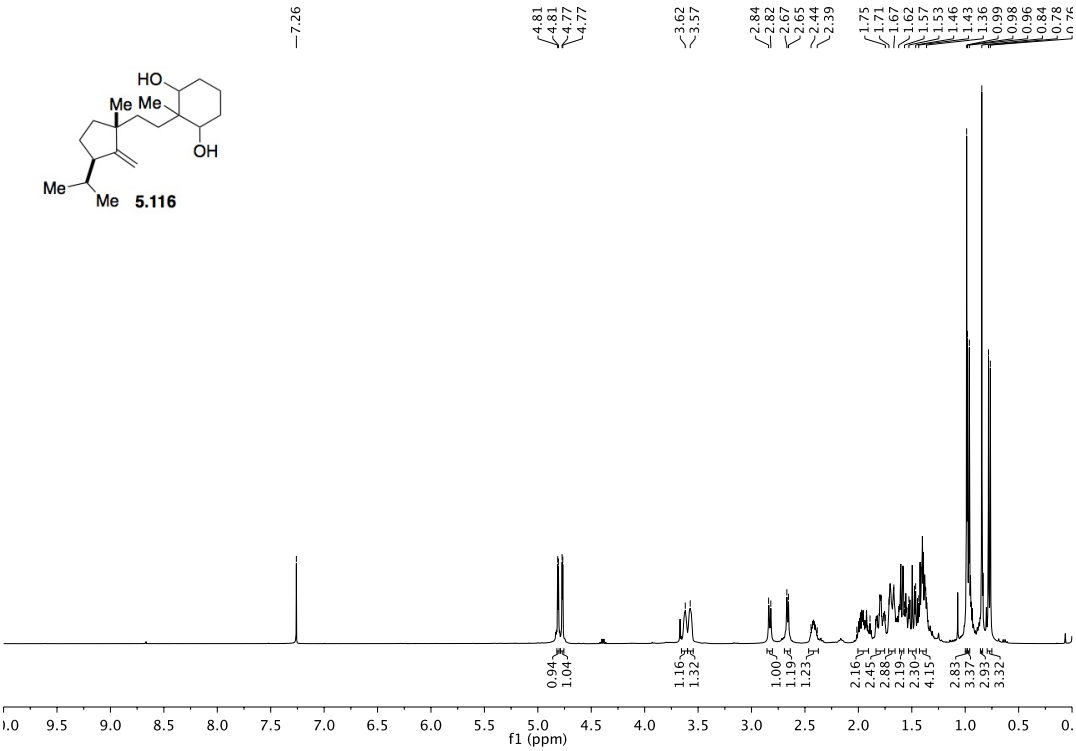
8.3.4 Synthetic Studies Towards Striatal A

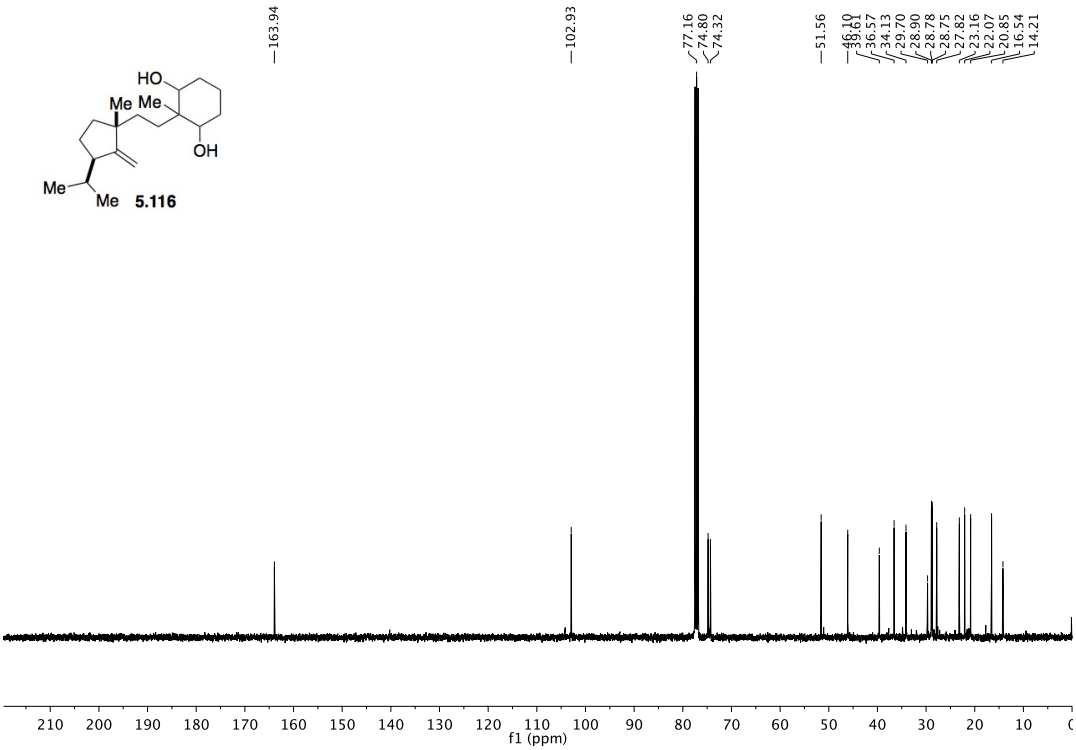


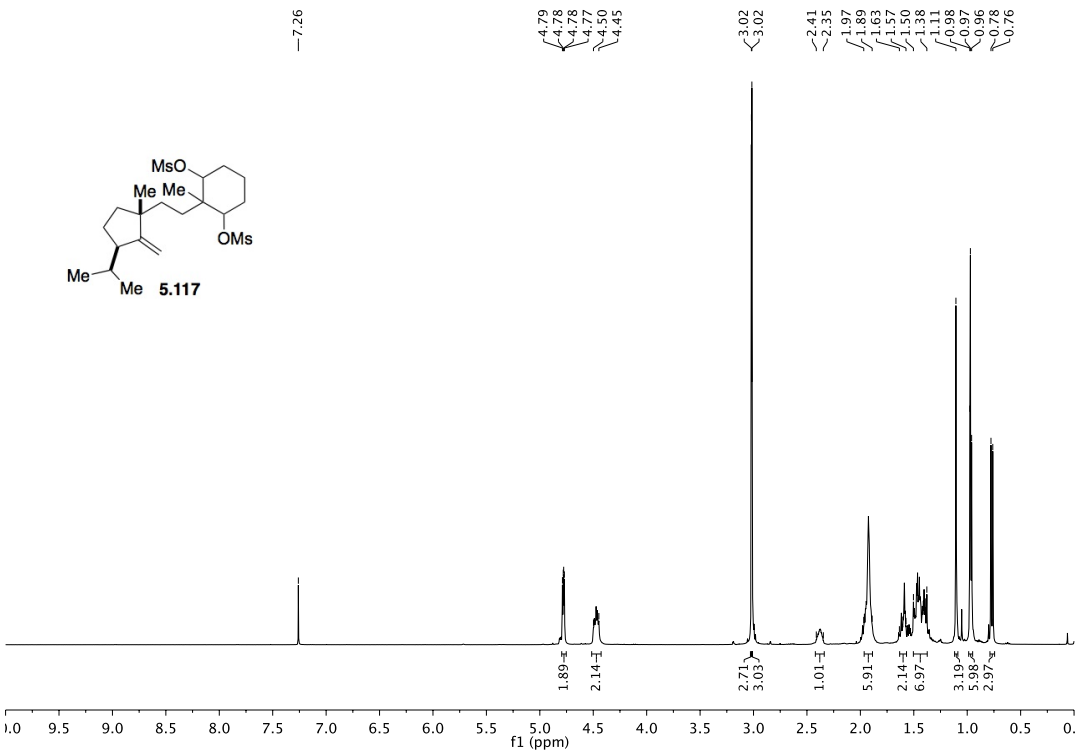


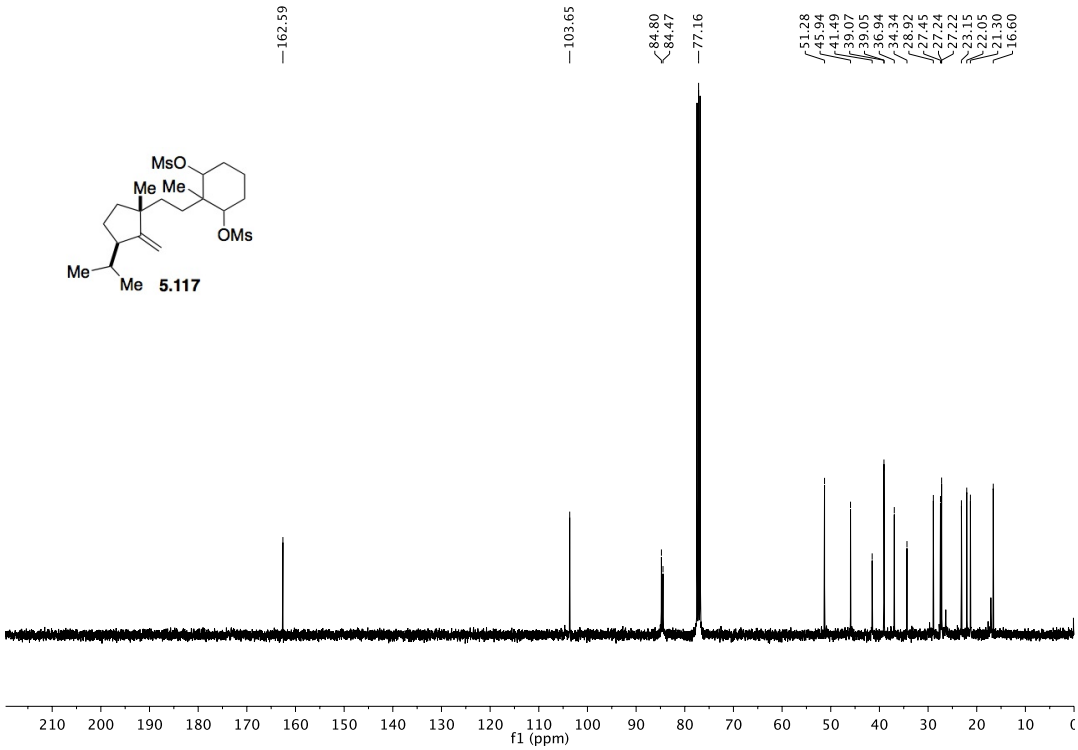

7.26
2.71
2.57
2.18
2.10
2.05
1.96
1.93
1.81
1.69
1.63
1.27
1.21
1.15
0.98
0.96
0.89
0.80
0.78
4.30
1.16
2.11
3.40
3.35
6.06
3.37
2.69
3.00
Me Me
O
O
O
Me
Me
5.111
f1 (ppm)

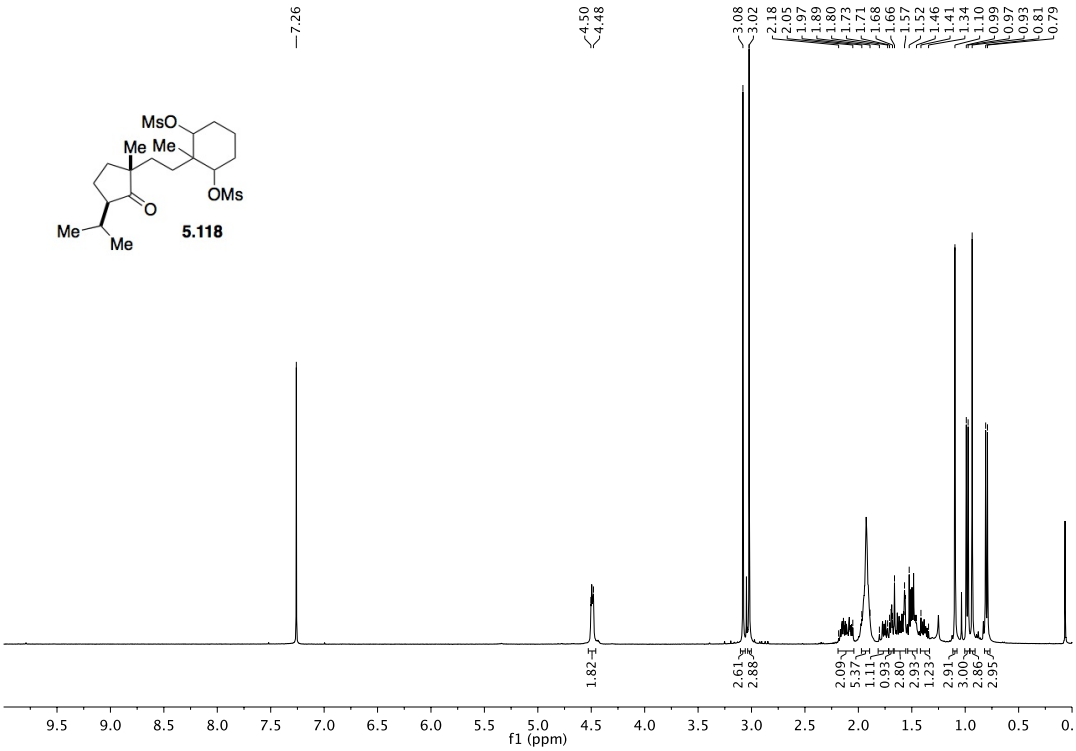

223.37
210.43
210.28
77.16
65.47
55.94
48.53
38.07
33.38
32.26
32.01
27.35
21.21
21.03
20.51
19.35
18.45
17.79
Me Me
O
O
O
Me
Me
5.111
f1 (ppm)

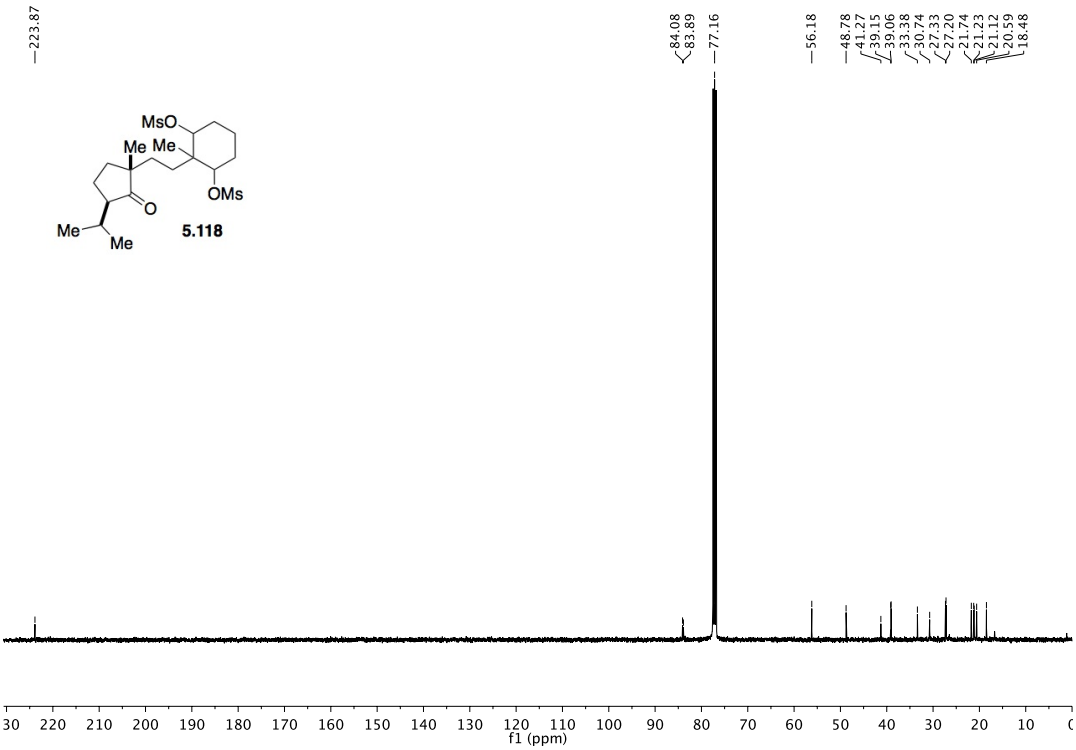

HO
Me Me
OH
Me
Me
5.116
7.26
4.81
4.81
4.77
4.77
3.62
3.57
2.84
2.82
2.67
2.65
2.44
2.39
1.75
1.71
1.67
1.62
1.57
1.53
1.46
1.43
1.36
0.99
0.98
0.96
0.84
0.78
0.94
1.04
1.16
1.32
1.00
1.19
1.23
2.16
2.45
2.88
2.19
2.30
4.15
2.83
3.37
2.93
3.32
f1 (ppm)

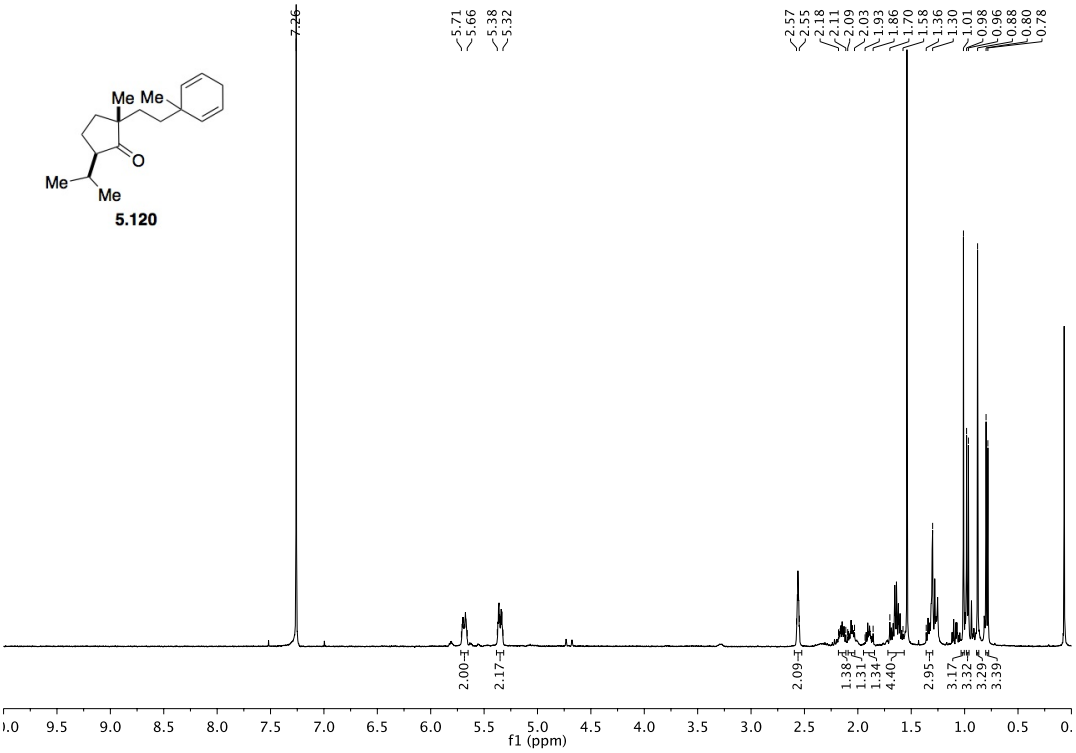

HO
Me Me
OH
Me
Me
5.116
163.94
102.93
77.16
74.80
74.32
51.56
46.10
39.61
36.57
34.13
29.70
28.90
28.78
28.75
27.82
23.16
22.07
20.85
16.54
14.21
f1 (ppm)

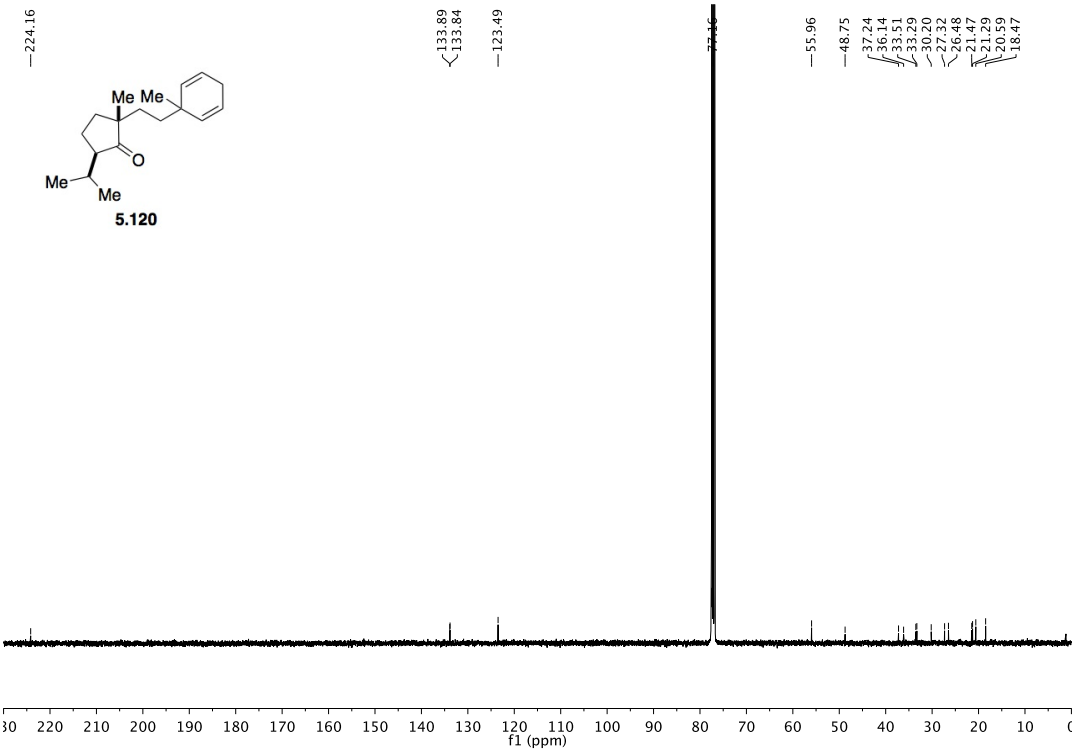

7.26
4.79
4.78
4.78
4.77
4.50
4.45
3.02
3.02
2.41
2.35
1.97
1.89
1.63
1.57
1.50
1.38
1.11
0.98
0.97
0.96
0.78
0.76
MsO
Me Me
OMs
Me
Me
5.117
1.89
2.14
2.71
3.03
1.01
5.91
2.14
6.97
3.19
5.98
2.97
f1 (ppm)

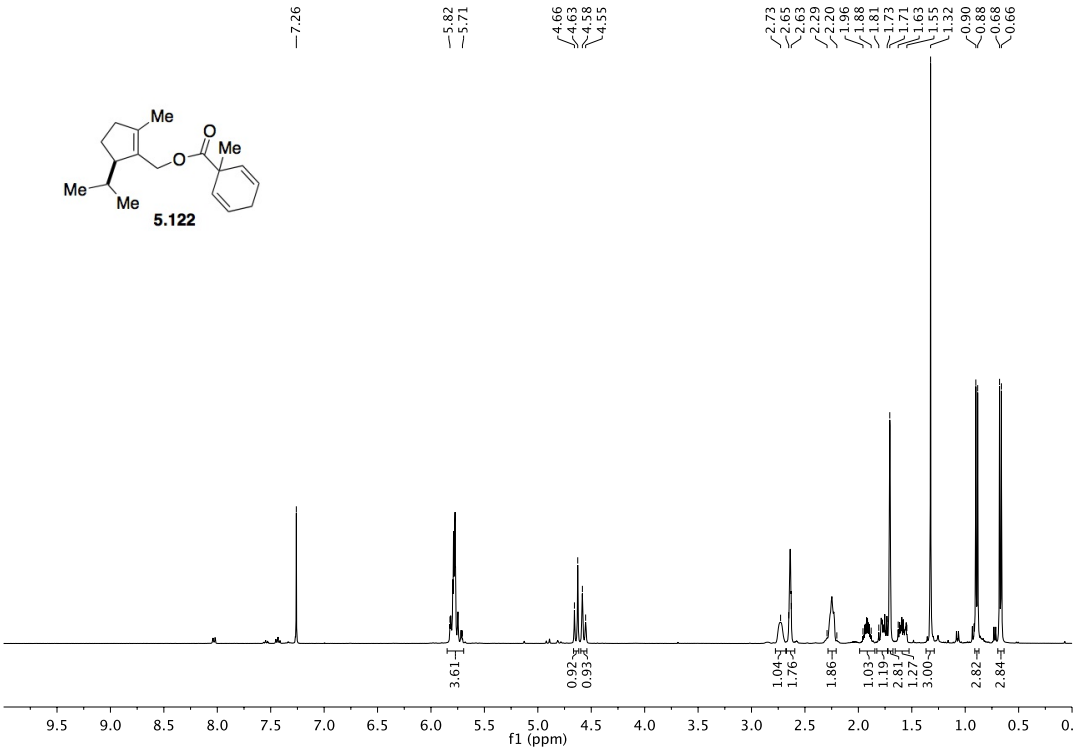

162.59
103.65
84.80
84.47
77.16
51.28
45.94
41.49
39.07
39.05
36.94
34.34
28.92
27.45
27.24
27.22
23.15
22.05
21.30
16.60
MsO
Me Me
OMs
Me
Me
5.117
f1 (ppm)

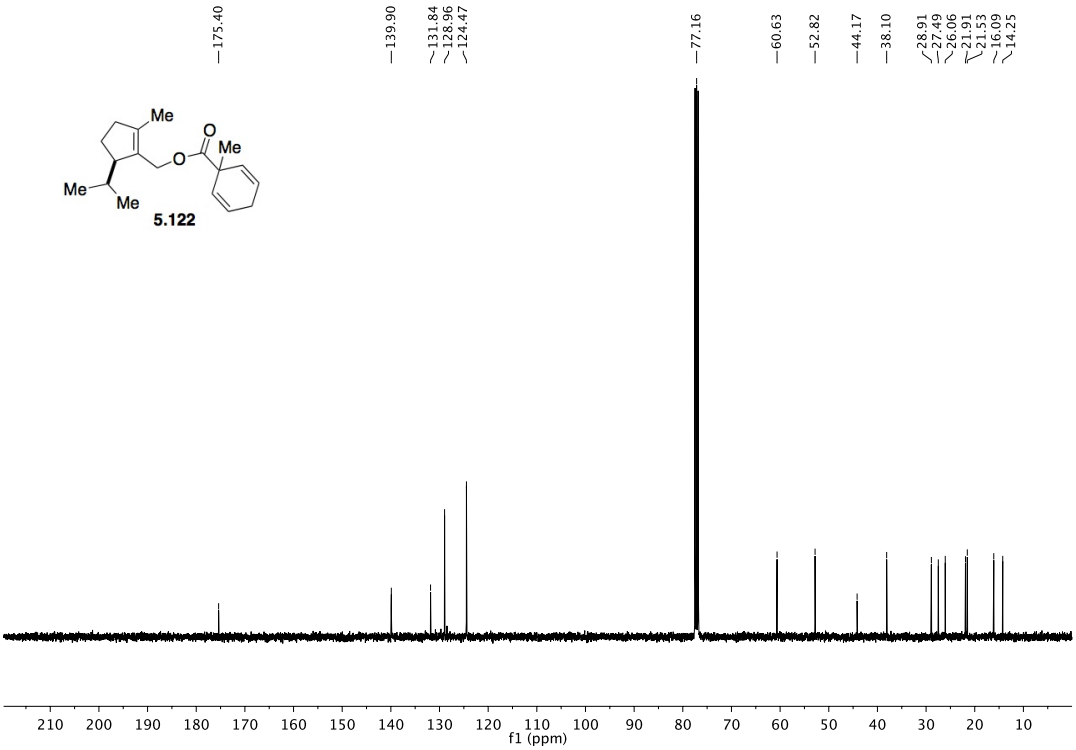

MsO
Me Me
OMs
O
Me
Me
5.118
f1 (ppm)

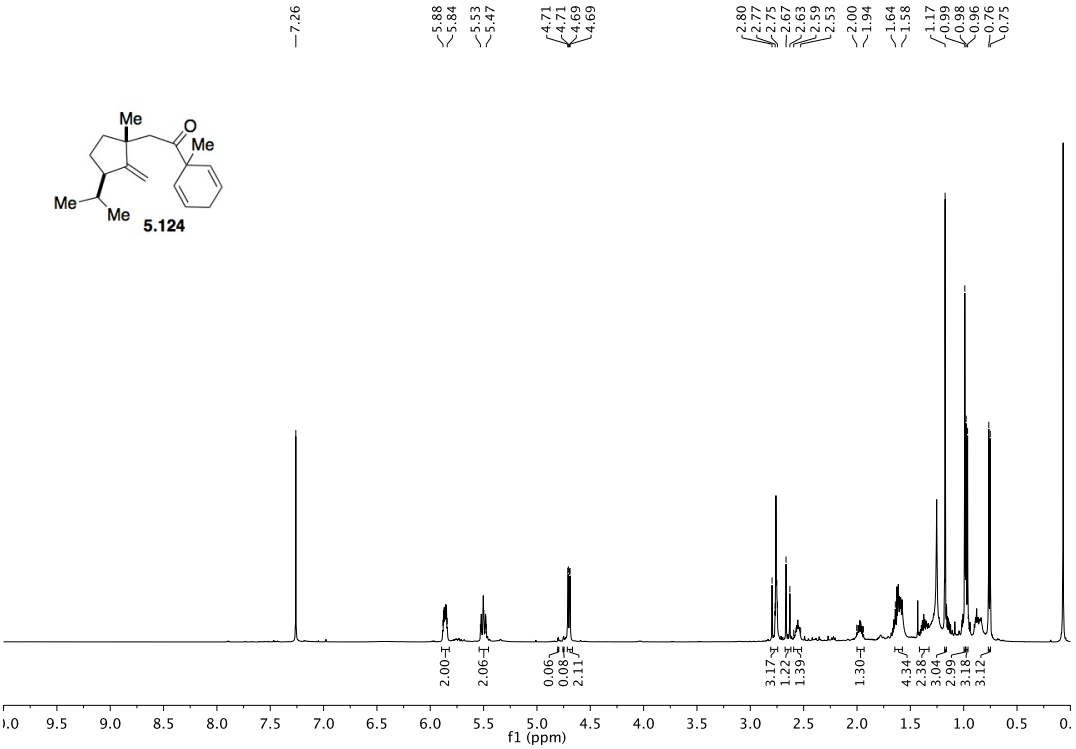

MsO
Me Me
OMs
O
Me
Me
5.118
f1 (ppm)

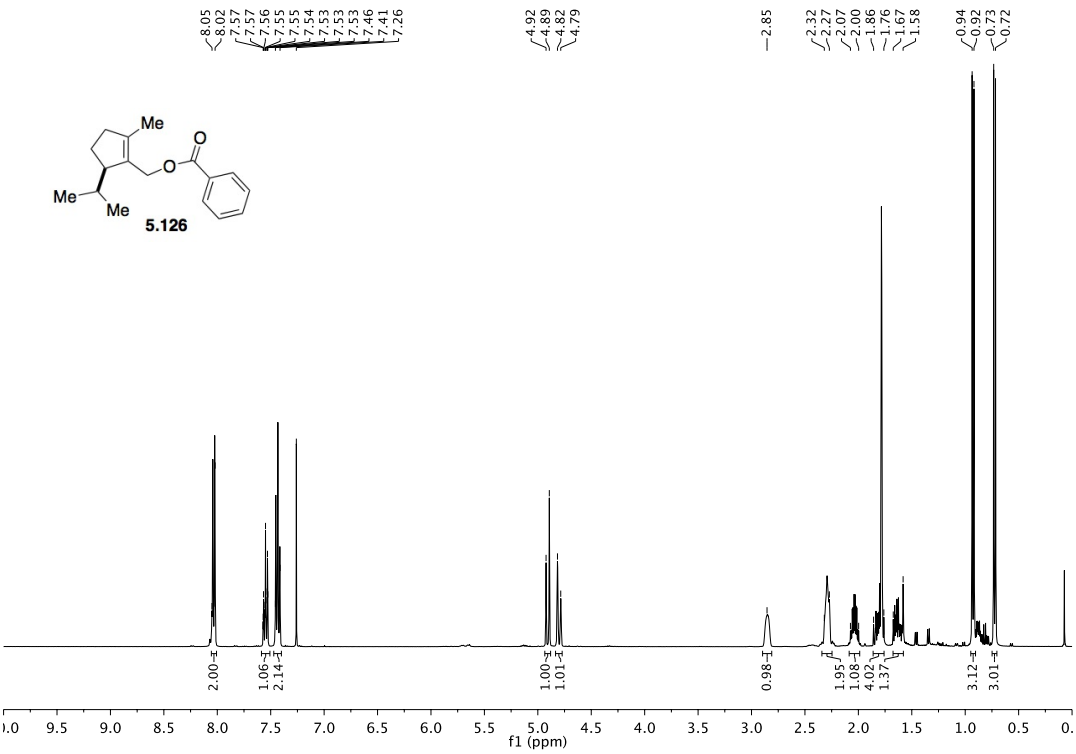

Me Me
O
Me
Me
5.120
7.26
5.71
5.66
5.38
5.32
2.57
2.55
2.18
2.11
2.09
2.03
1.93
1.86
1.70
1.58
1.36
1.30
1.01
0.98
0.96
0.88
0.80
0.78
2.00
2.17
2.09
1.38
1.31
1.34
4.40
2.95
3.17
3.32
3.29
3.39
f1 (ppm)

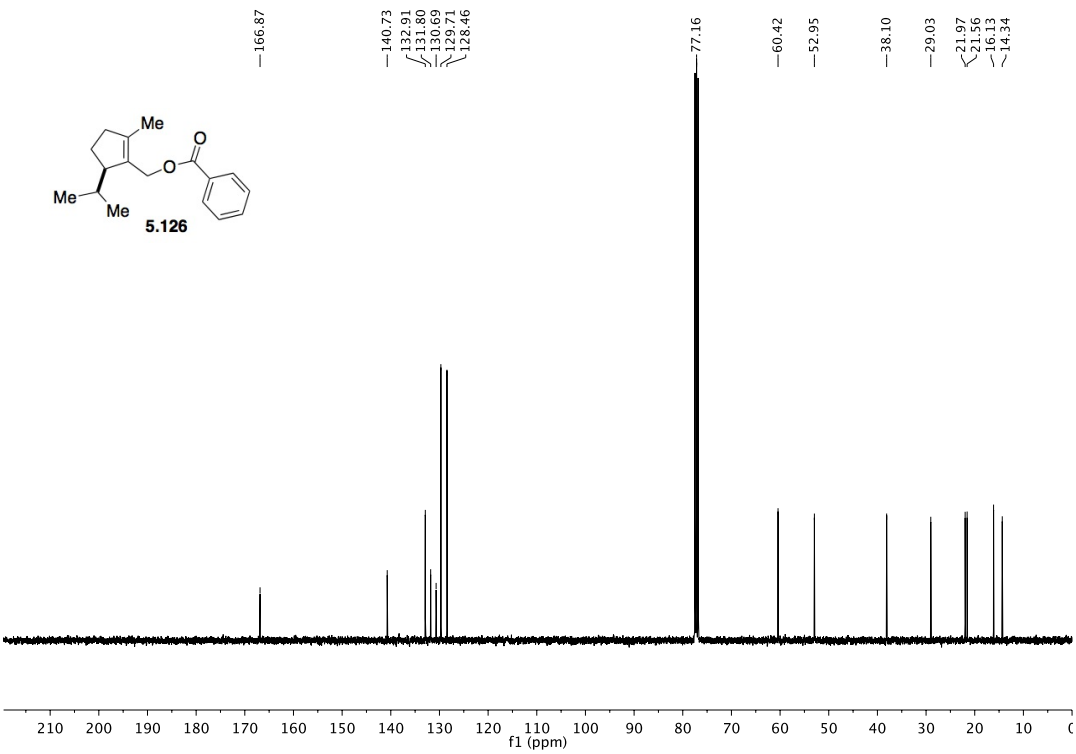

224.16
133.89
133.84
123.49
77.16
55.96
48.75
37.24
36.14
33.51
33.29
30.20
27.32
26.48
21.47
21.29
20.59
18.47
Me Me
O
Me
Me
5.120
f1 (ppm)

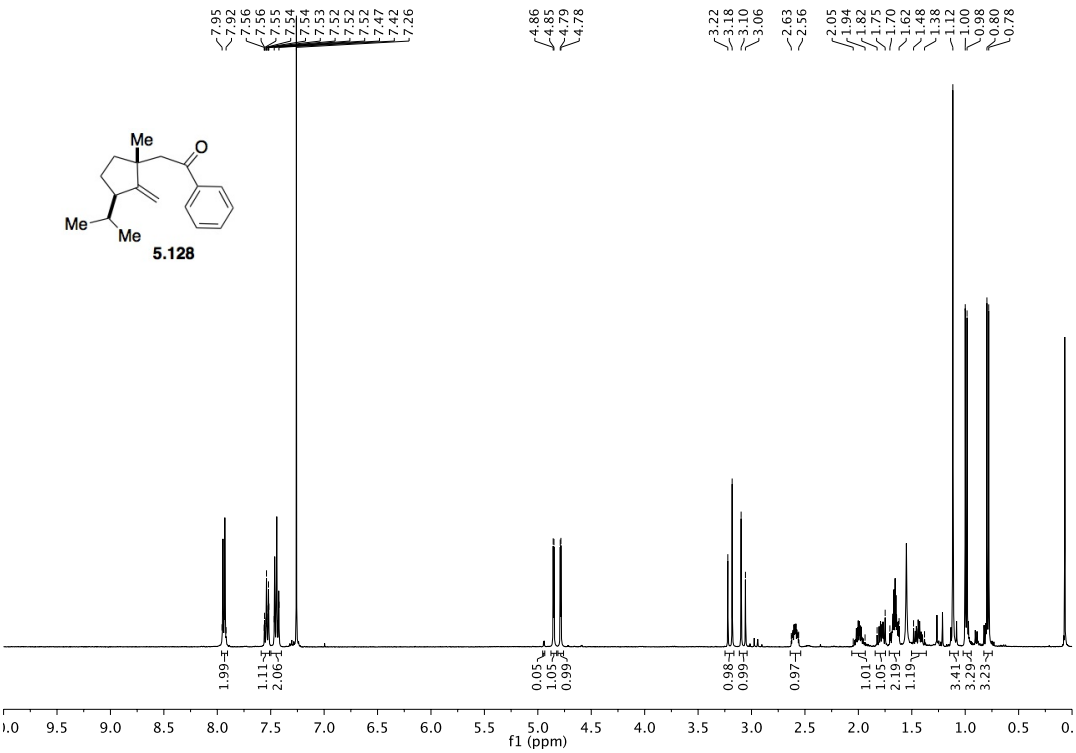

7.26
5.82
5.71
4.66
4.63
4.58
4.55
2.73
2.65
2.63
2.29
2.20
1.96
1.88
1.81
1.73
1.71
1.63
1.55
1.32
0.90
0.88
0.68
0.66
Me
O
Me
Me
Me
5.122
3.61
0.92
0.93
1.04
1.76
1.86
1.03
1.19
2.81
1.27
3.00
2.82
2.84
f1 (ppm)

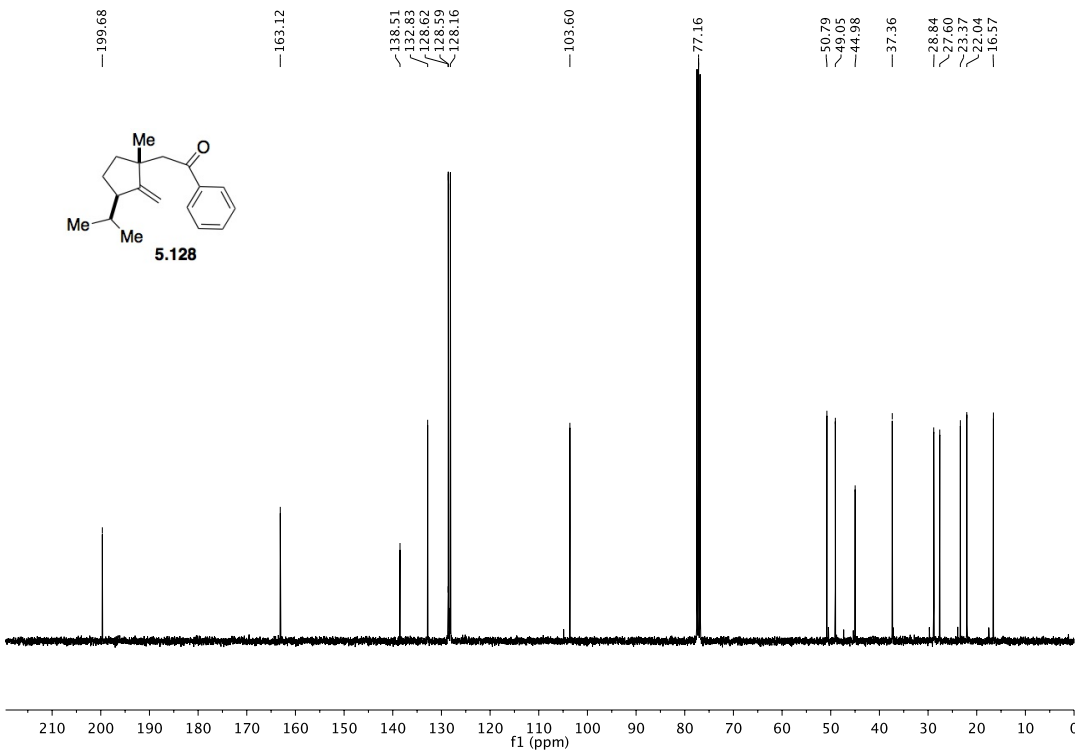

175.40
139.90
131.84
128.96
124.47
77.16
60.63
52.82
44.17
38.10
28.91
27.49
26.06
21.91
21.53
16.09
14.25
Me
O
Me
Me
Me
5.122
f1 (ppm)

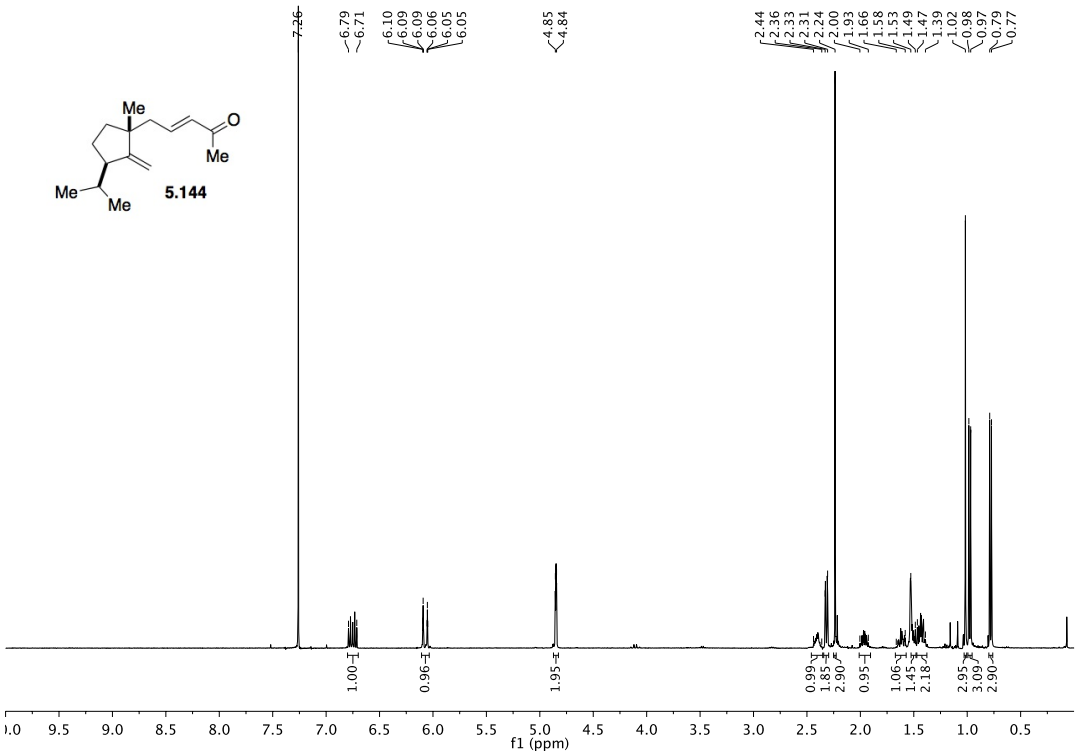

7.26
5.88
5.84
5.53
5.47
4.71
4.71
4.69
4.69
2.80
2.77
2.75
2.67
2.63
2.59
2.53
2.00
1.94
1.64
1.58
1.17
0.99
0.98
0.96
0.76
0.75
Me
O
Me
Me
Me
5.124
2.00
2.06
0.06
0.08
2.11
3.17
1.22
1.39
1.30
4.34
2.38
3.04
2.99
3.18
3.12
f1 (ppm)

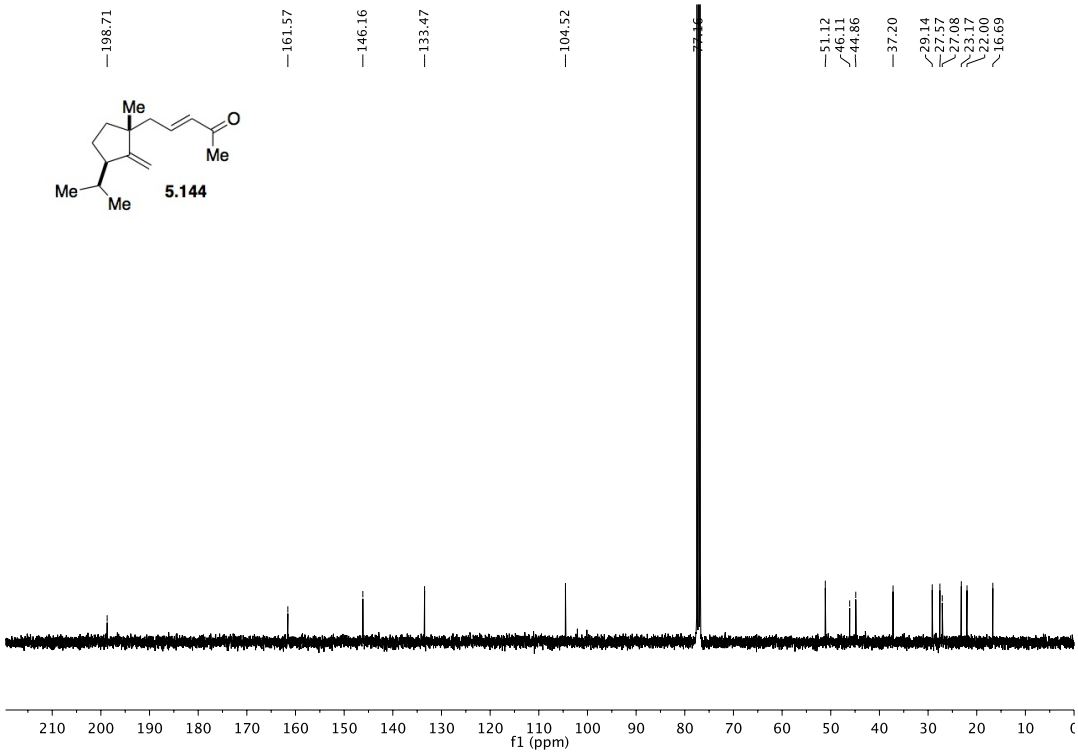

8.05
8.02
7.57
7.57
7.56
7.55
7.55
7.54
7.53
7.53
7.53
7.46
7.41
7.26
4.92
4.89
4.82
4.79
2.85
2.32
2.27
2.07
2.00
1.86
1.76
1.67
1.58
0.94
0.92
0.73
0.72
Me
O
O
Me
Me
5.126
2.00
1.06
2.14
1.00
1.01
0.98
1.95
1.08
4.02
1.37
3.12
3.01
f1 (ppm)


166.87
140.73
132.91
131.80
130.69
129.71
128.46
77.16
60.42
52.95
38.10
29.03
21.97
21.56
16.13
14.34
Me
O
O
Me
Me
5.126
f1 (ppm)


7.95
7.92
7.56
7.56
7.55
7.54
7.54
7.53
7.52
7.52
7.52
7.47
7.42
7.26
4.86
4.85
4.79
4.78
3.22
3.18
3.10
3.06
2.63
2.56
2.05
1.94
1.82
1.75
1.70
1.62
1.48
1.38
1.12
1.00
0.98
0.80
0.78
Me
O
Me
Me
5.128
1.99
1.11
2.06
0.05
1.05
0.99
0.98
0.99
0.97
1.01
1.05
2.19
1.19
3.41
3.29
3.23
f1 (ppm)


199.68
163.12
138.51
132.83
128.62
128.59
128.16
103.60
77.16
50.79
49.05
44.98
37.36
28.84
27.60
23.37
22.04
16.57
Me
O
Me
Me
5.128
f1 (ppm)


7.26
6.79
6.71
6.10
6.09
6.09
6.06
6.05
6.05
4.85
4.84
2.44
2.36
2.33
2.31
2.24
2.00
1.93
1.66
1.58
1.53
1.49
1.47
1.39
1.02
0.98
0.97
0.79
0.77
Me
O
Me
Me
Me
5.144
1.00
0.96
1.95
0.99
1.85
2.90
0.95
1.06
1.45
2.18
2.95
3.09
2.90
f1 (ppm)


198.71
161.57
146.16
133.47
104.52
77.16
51.12
46.11
44.86
37.20
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27.08
23.17
22.00
16.69
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O
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Me
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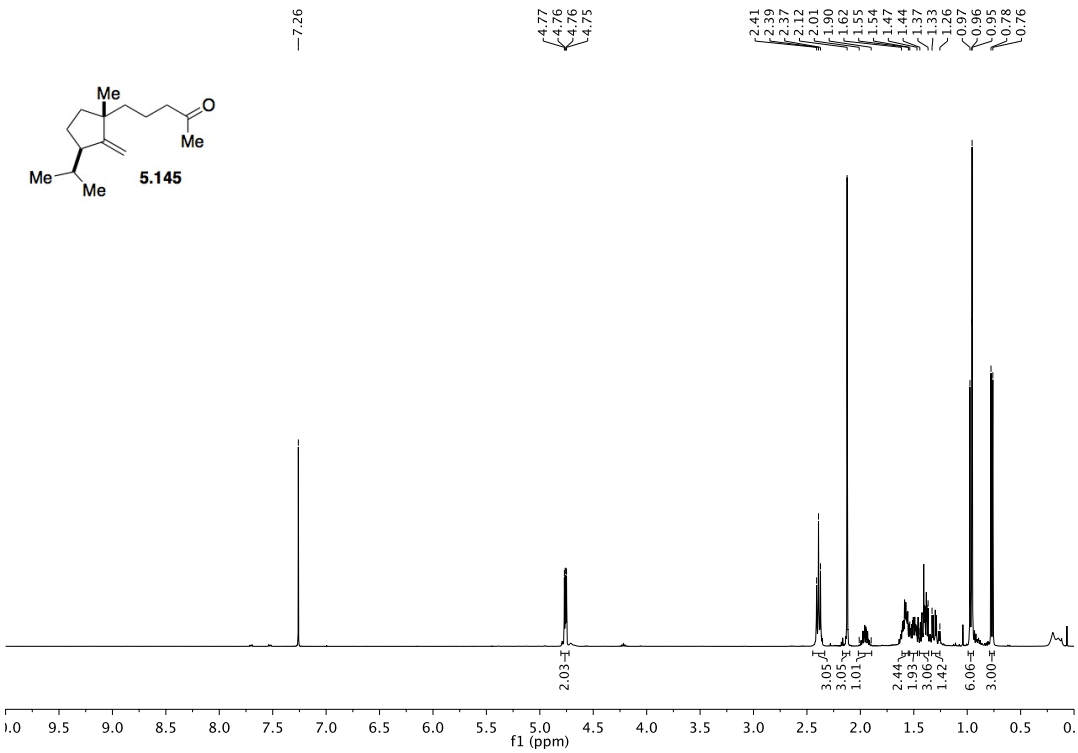
f1 (ppm)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4.76
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4.75
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2.39
2.37
2.12
2.01
1.90
1.62
1.55
1.54
1.47
1.44
1.37
1.33
1.26
0.97
0.96
0.95
0.78
0.76
Me
O
Me
Me
Me
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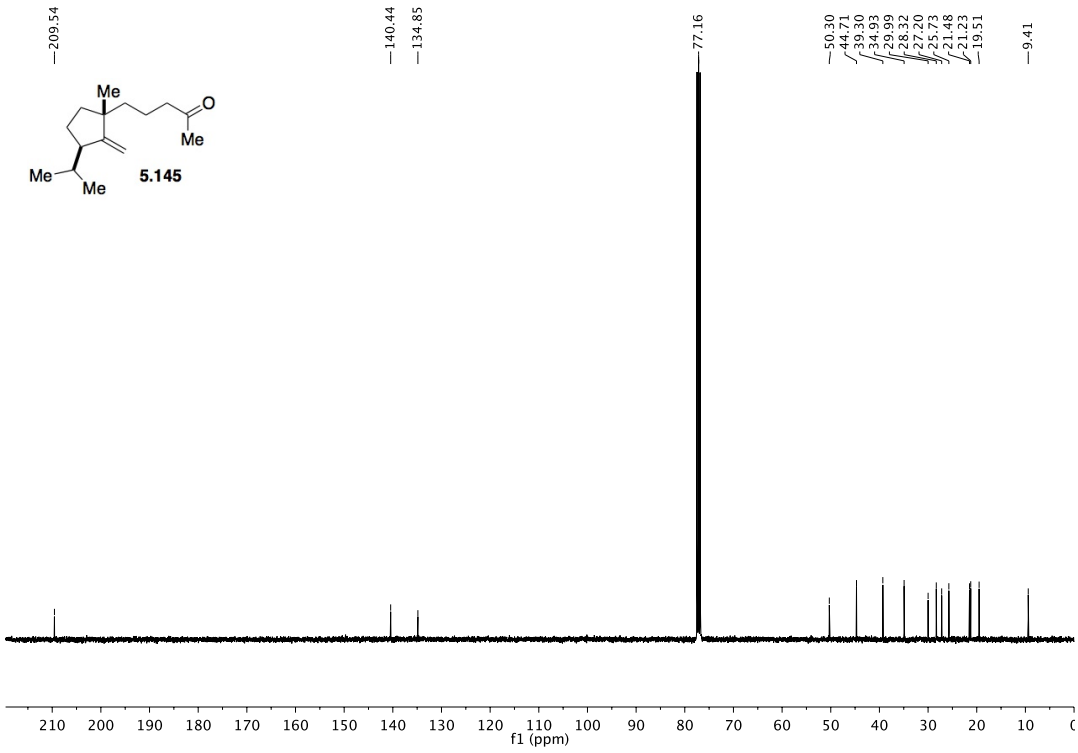
3.05
1.01
2.44
1.93
3.06
1.42
6.06
3.00
f1 (ppm)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77.16
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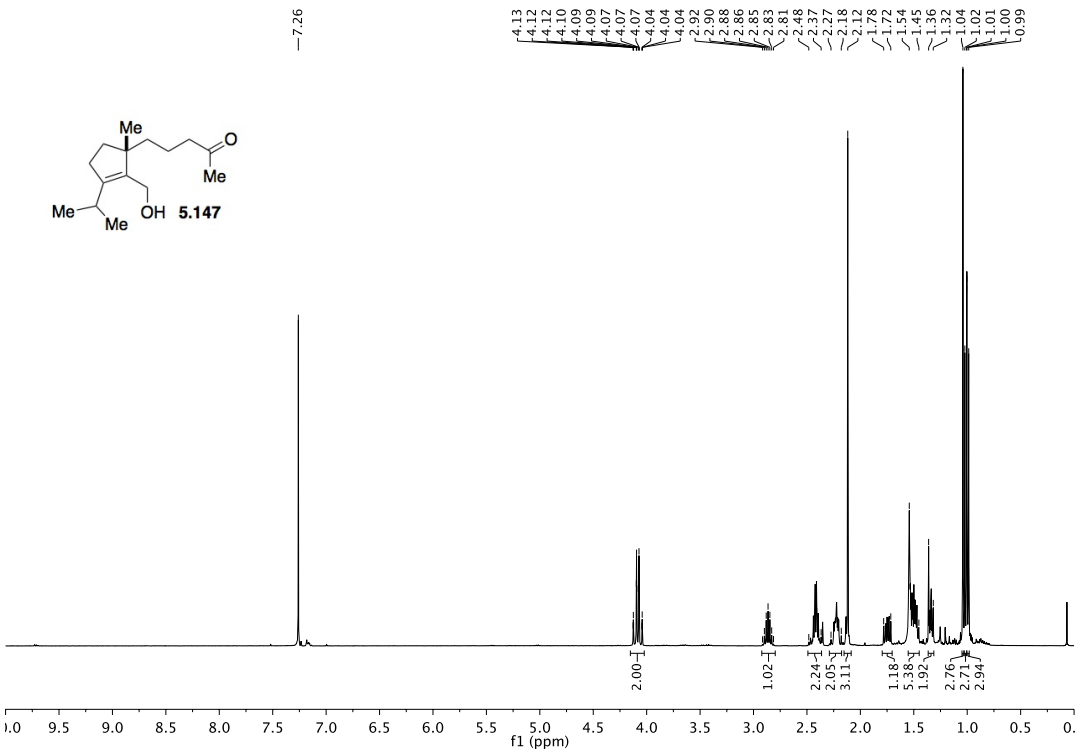
44.71
39.30
34.93
29.99
28.32
27.20
25.73
21.48
21.23
19.51
9.41
Me
O
Me
Me
Me
5.145
f1 (ppm)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4.12
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4.09
4.09
4.07
4.07
4.07
4.04
4.04
4.04
2.92
2.90
2.88
2.86
2.85
2.83
2.81
2.48
2.37
2.27
2.18
2.12
1.78
1.72
1.54
1.45
1.36
1.32
1.04
1.02
1.01
1.00
0.99
Me
O
Me
Me
Me
OH
5.147
2.00
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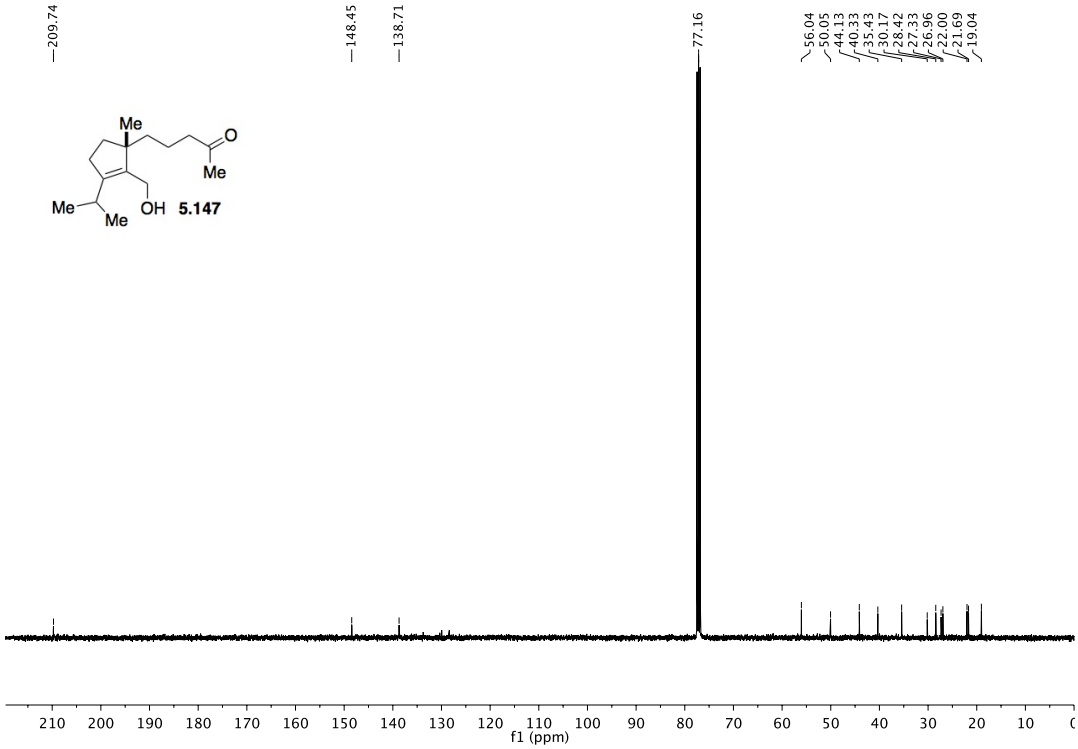
2.05
3.11
1.18
5.38
1.92
2.76
2.71
2.94
f1 (ppm)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50.05
44.13
40.33
35.43
30.17
28.42
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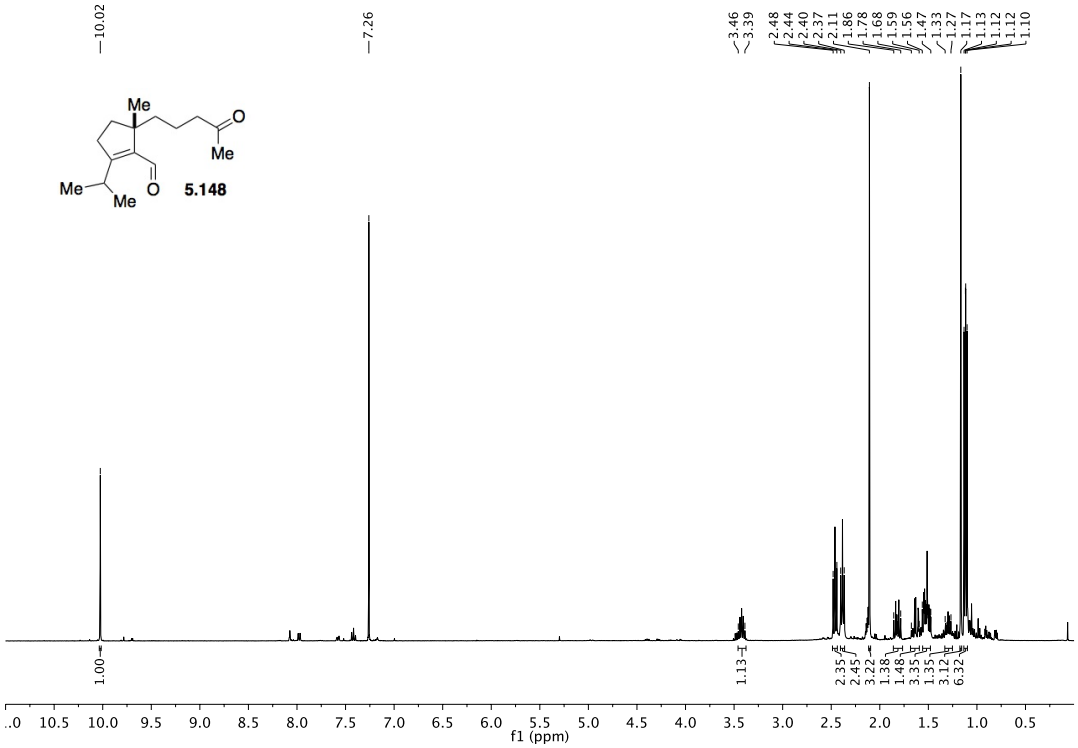
26.96
22.00
21.69
19.04
Me
O
Me
Me
Me
OH
5.147
f1 (ppm)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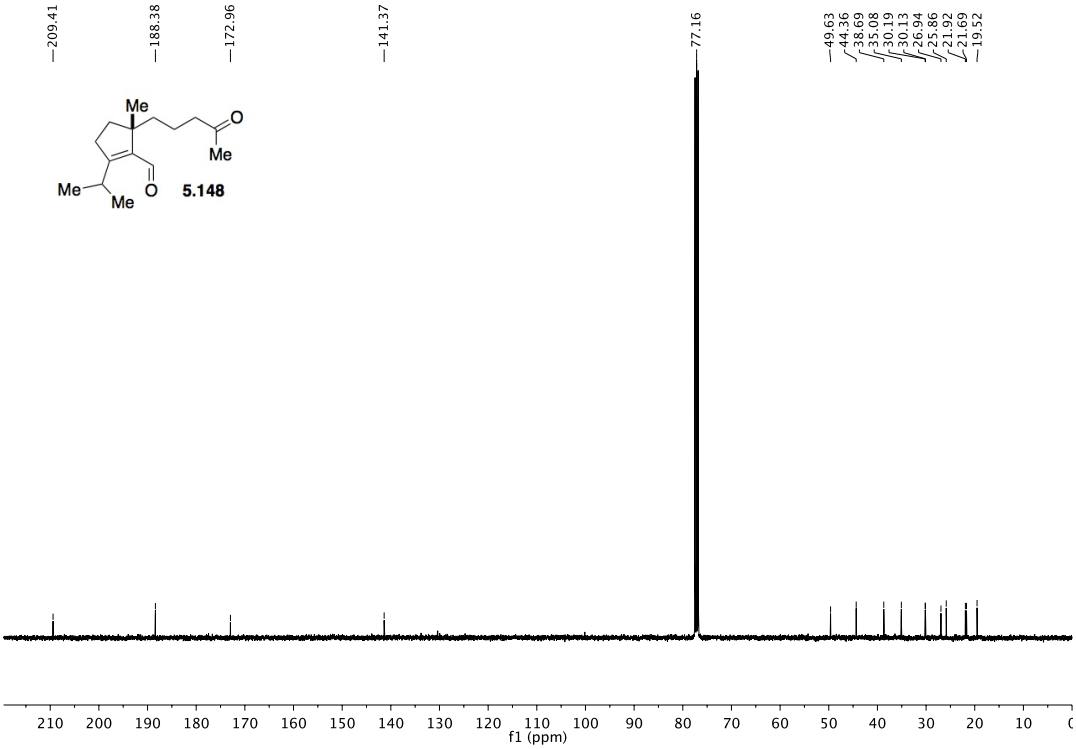
7.26
3.46
3.39
2.48
2.44
2.40
2.37
2.11
1.86
1.78
1.68
1.59
1.56
1.47
1.33
1.27
1.17
1.13
1.12
1.12
1.10
Me
O
Me
Me
Me
O
5.148
1.00
1.13
2.35
2.45
3.22
1.38
1.48
3.35
1.35
3.12
6.32
f1 (ppm)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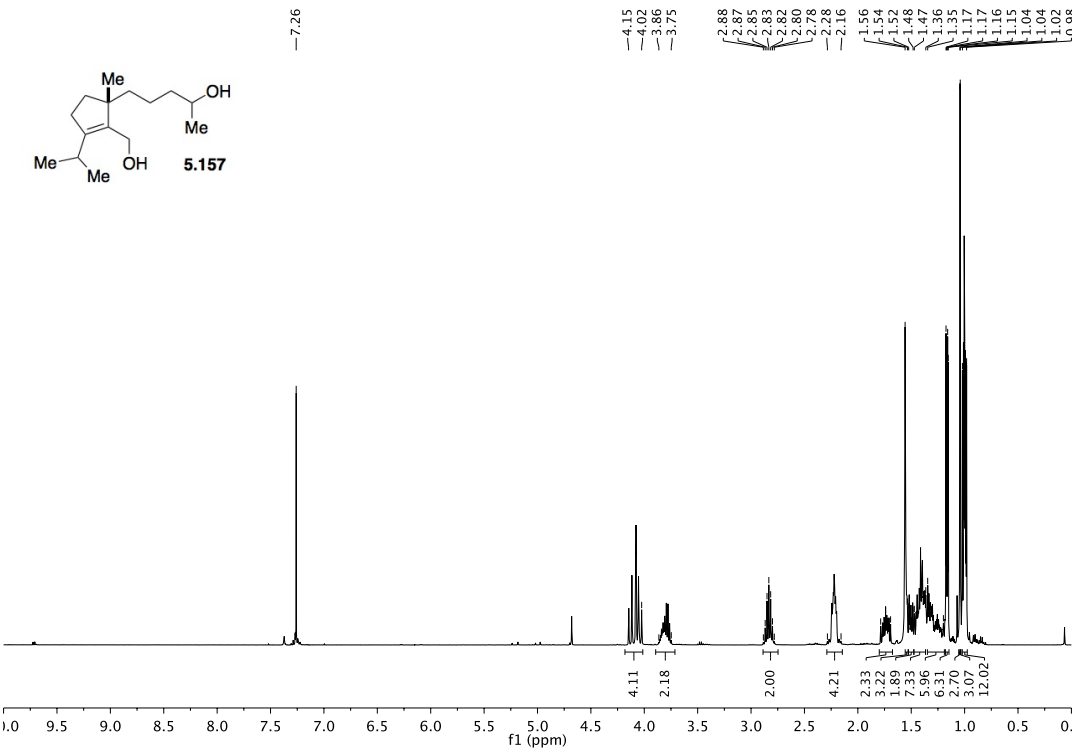
141.37
77.16
49.63
44.36
38.69
35.08
30.19
30.13
26.94
25.86
21.92
21.69
19.52
Me
O
Me
Me
Me
O
5.148
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)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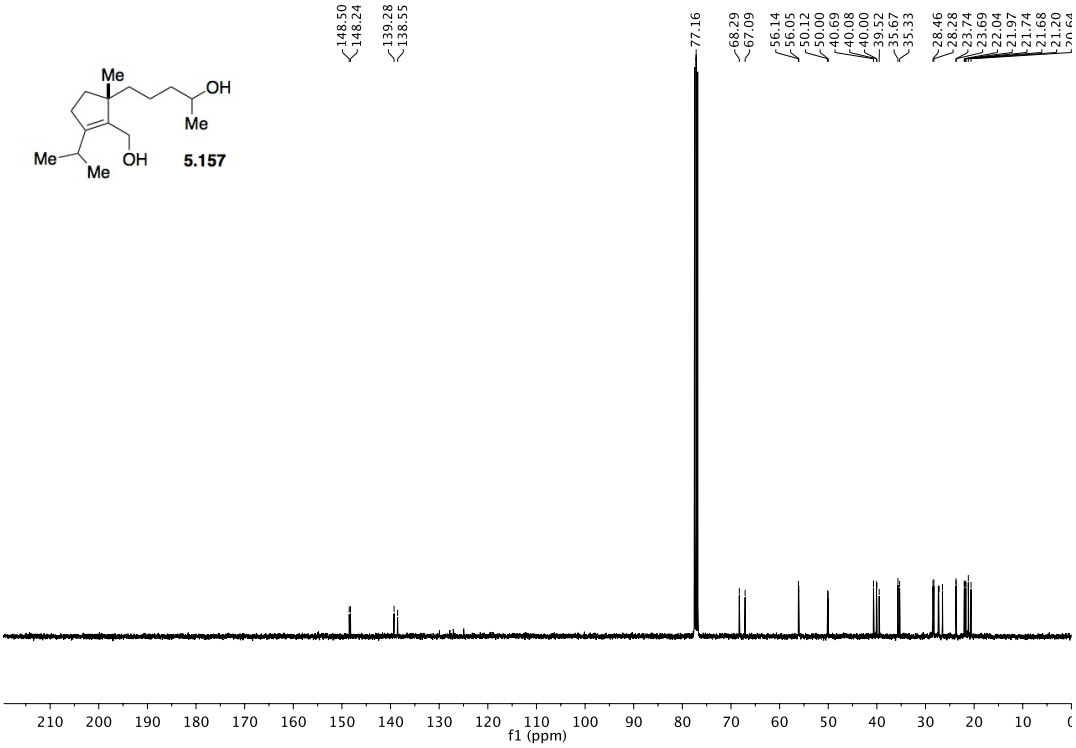
4.02
3.86
3.75
2.88
2.87
2.85
2.83
2.82
2.80
2.78
2.28
2.16
1.56
1.54
1.52
1.48
1.47
1.36
1.35
1.17
1.16
1.15
1.04
1.04
1.02
Me
OH
Me
Me
OH
5.157
4.11
2.18
2.00
4.21
2.33
3.22
1.89
7.33
5.96
6.31
2.70
3.07
12.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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148.24
139.28
138.55
77.16
68.29
67.09
56.14
56.05
50.12
50.00
40.69
40.08
40.00
39.52
35.67
35.33
28.46
28.28
23.74
23.69
22.04
21.97
21.74
21.68
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Me
Me
OH
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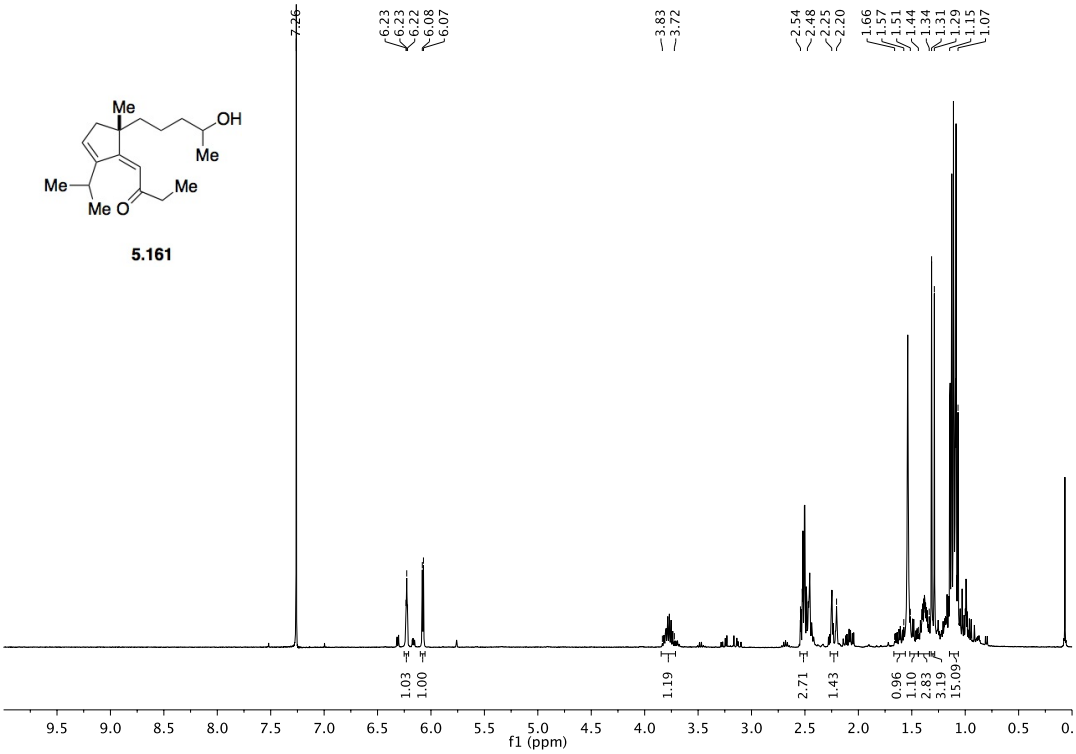
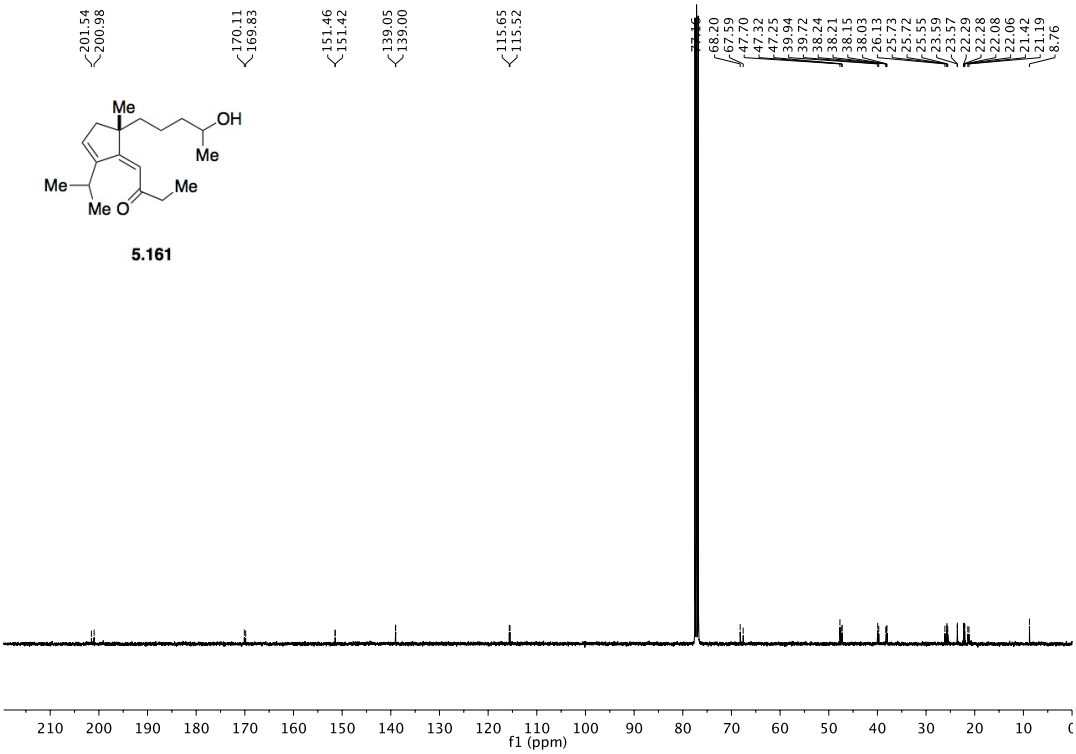
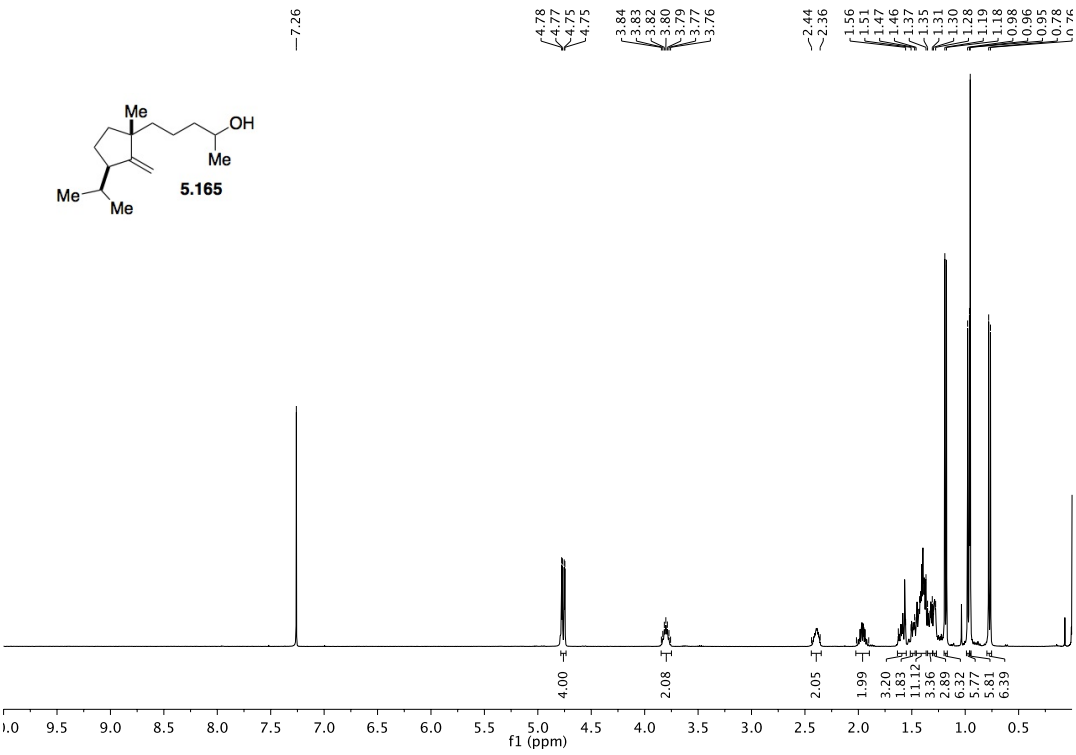
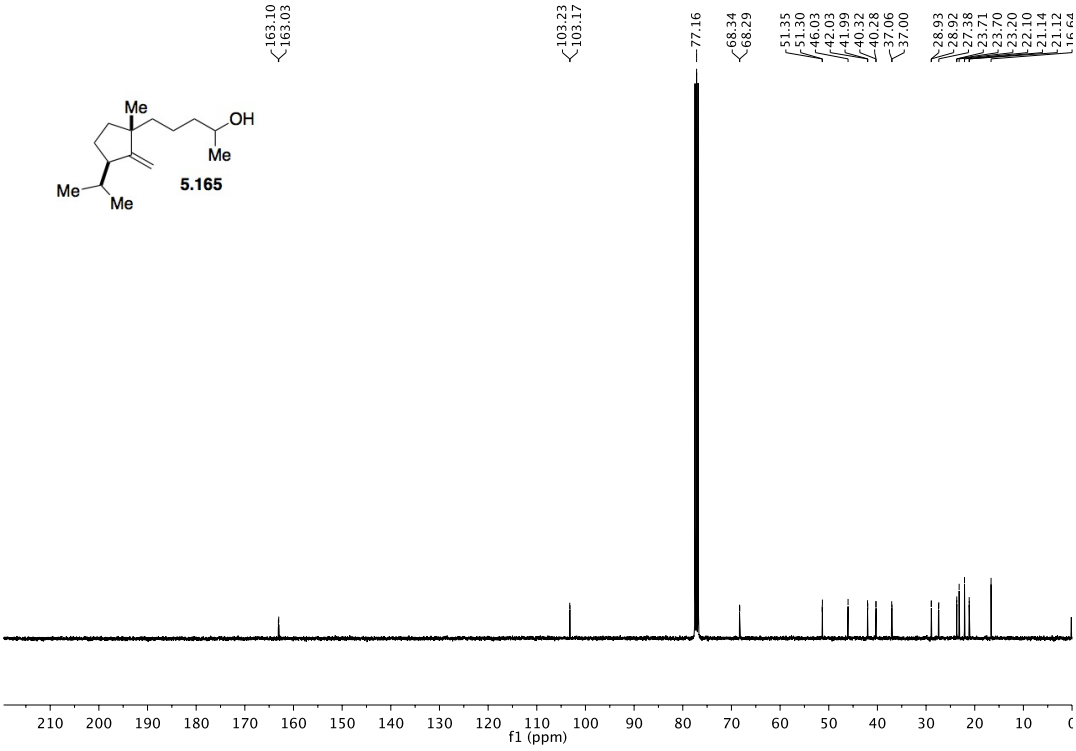
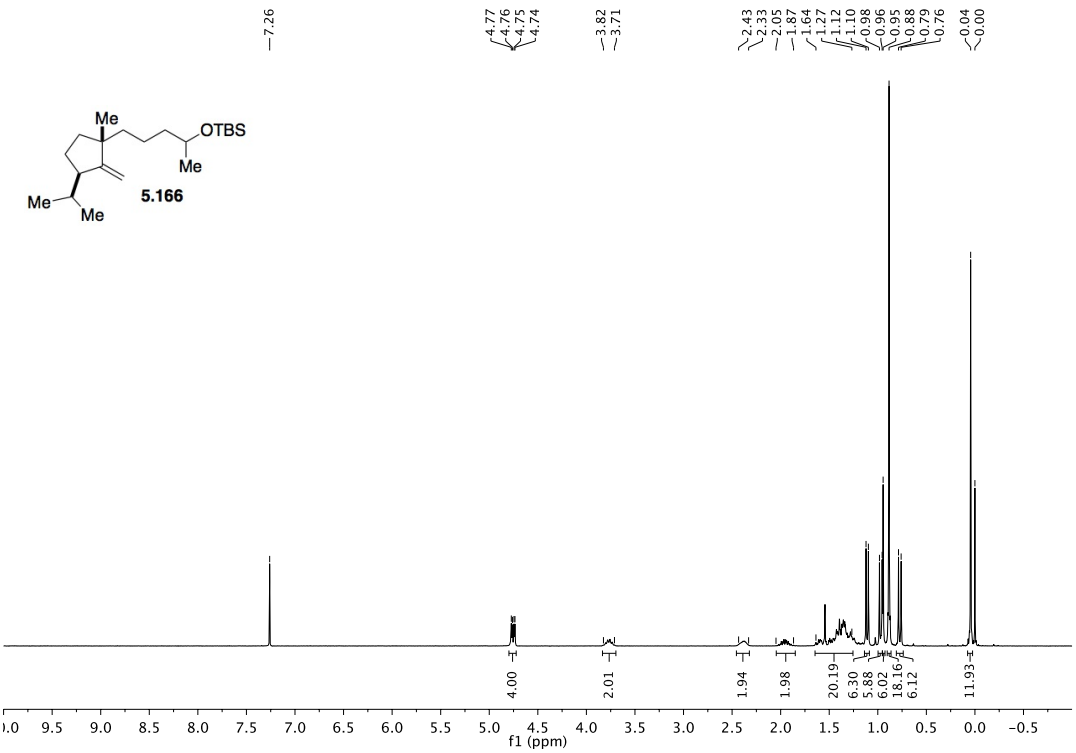
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

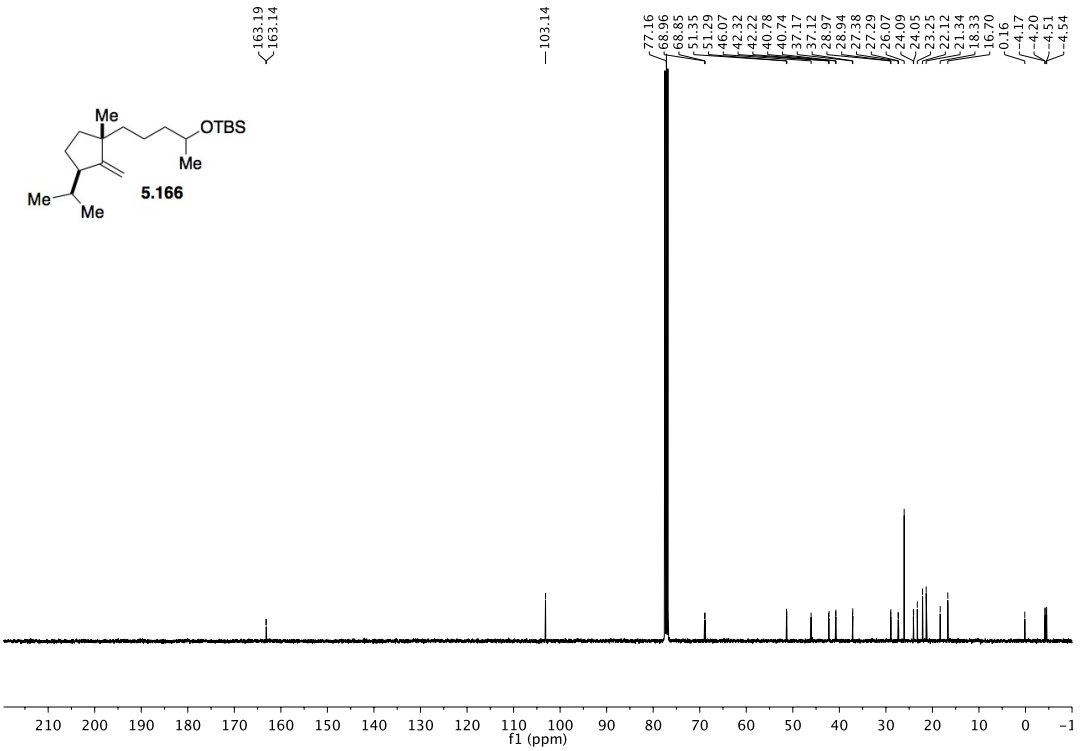

7.26
6.23
6.23
6.22
6.08
6.07
3.83
3.72
2.54
2.48
2.25
2.20
1.66
1.57
1.51
1.44
1.34
1.31
1.29
1.15
1.07
Me
OH
Me
Me
Me
Me
O
5.161
1.03
1.00
1.19
2.71
1.43
0.96
1.10
2.83
3.19
15.09
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

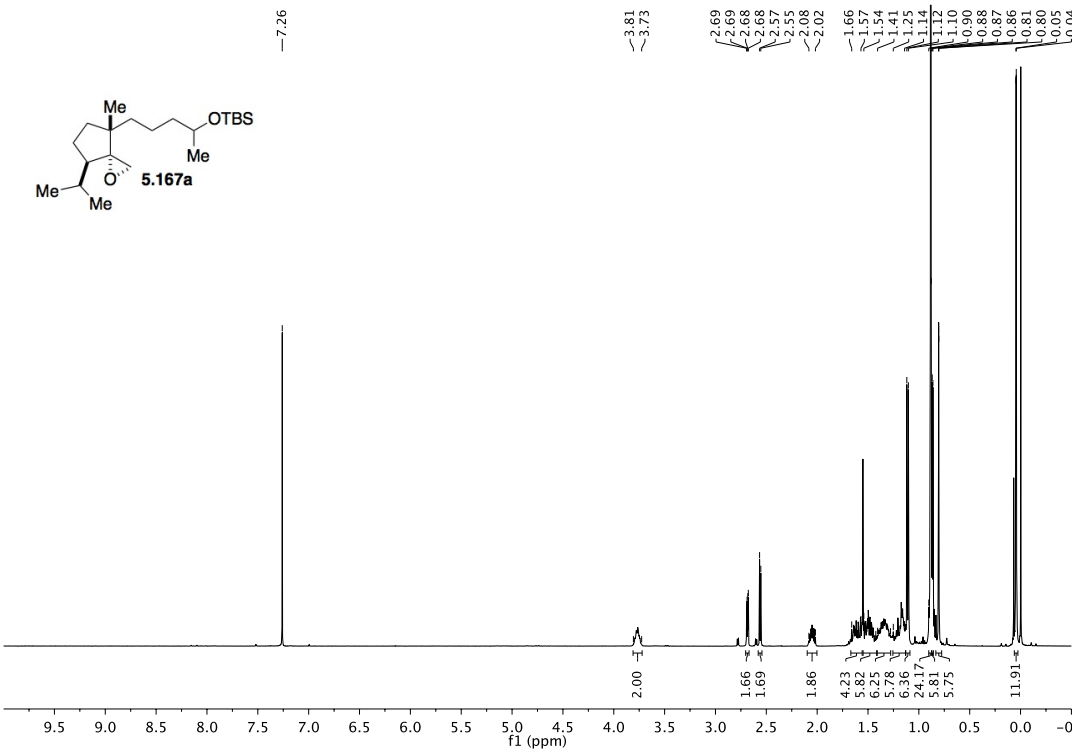

201.54
200.98
170.11
169.83
151.46
151.42
139.05
139.00
115.65
115.52
77.16
68.20
67.59
47.70
47.32
47.25
39.94
39.72
38.24
38.21
38.15
38.03
26.13
25.73
25.72
25.55
23.59
23.57
22.29
22.28
22.08
22.06
21.42
21.19
8.76
Me
OH
Me
Me
Me O
Me
5.161
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

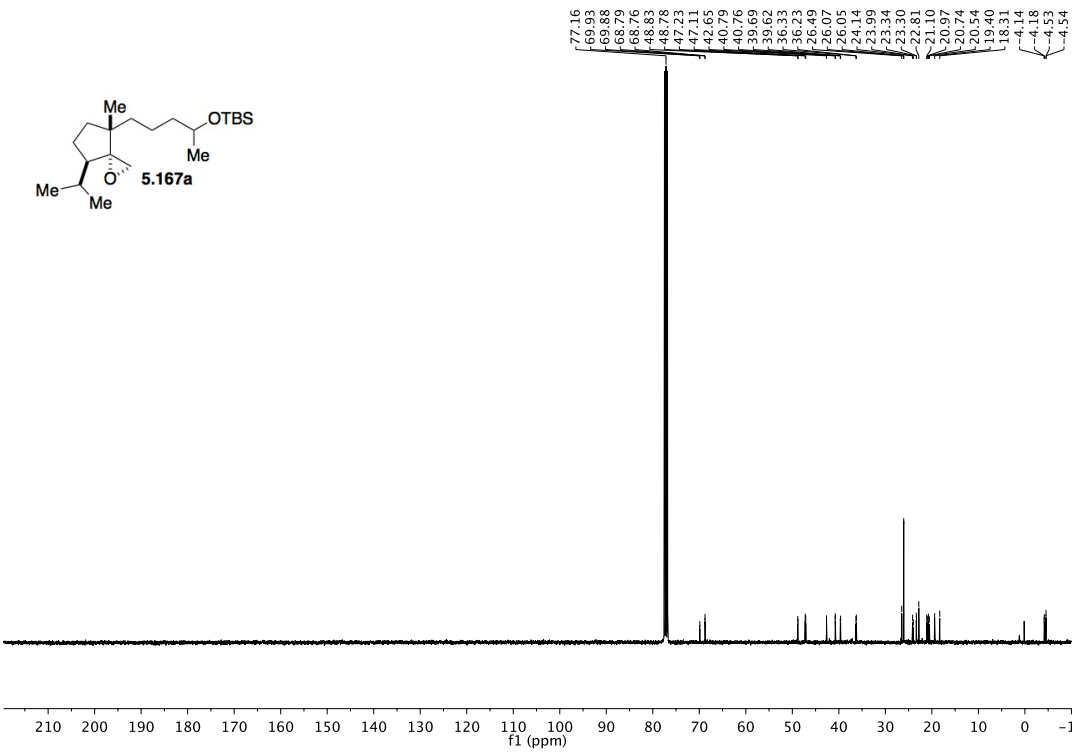

7.26
4.78
4.77
4.75
4.75
3.84
3.83
3.82
3.80
3.79
3.77
3.76
2.44
2.36
1.56
1.51
1.47
1.46
1.37
1.35
1.31
1.30
1.28
1.19
1.18
0.98
0.96
0.95
0.78
Me
OH
Me
Me
Me
5.165
4.00
2.08
2.05
1.99
3.20
1.83
11.12
3.36
2.89
6.32
5.77
5.81
6.39
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

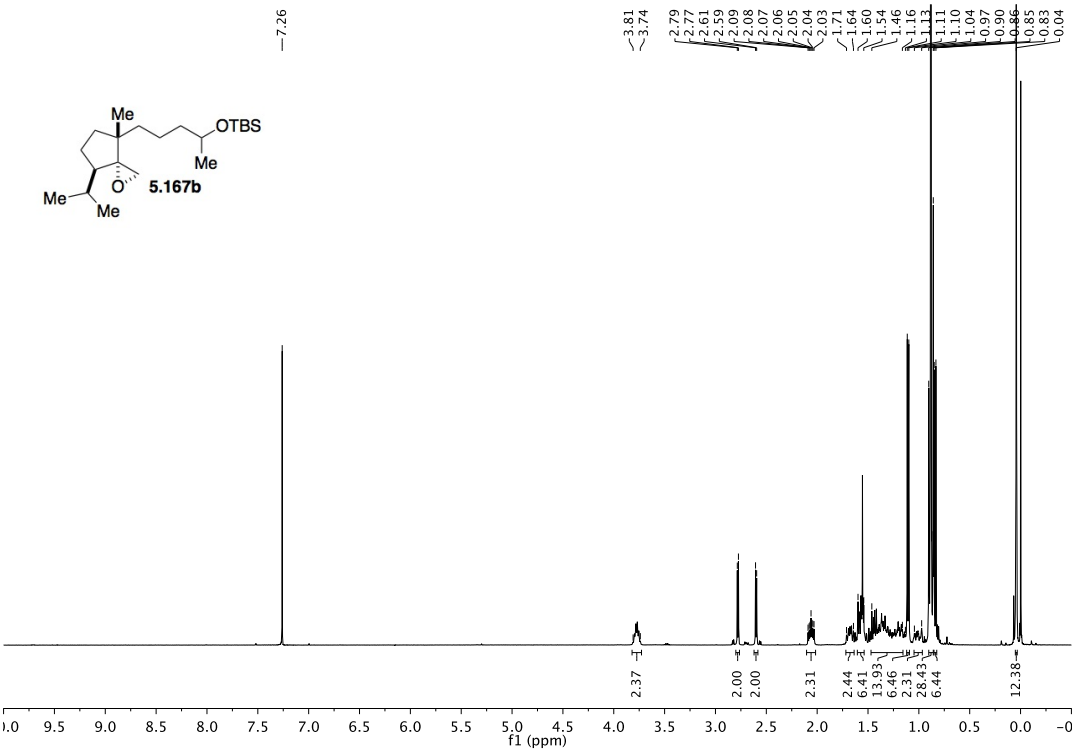

163.10
163.03
103.23
103.17
77.16
68.34
68.29
51.35
51.30
46.03
42.03
41.99
40.32
40.28
37.06
37.00
28.93
28.92
27.38
23.71
23.70
23.20
22.10
21.14
21.12
Me
OH
Me
Me
Me
5.165
f1 (ppm)

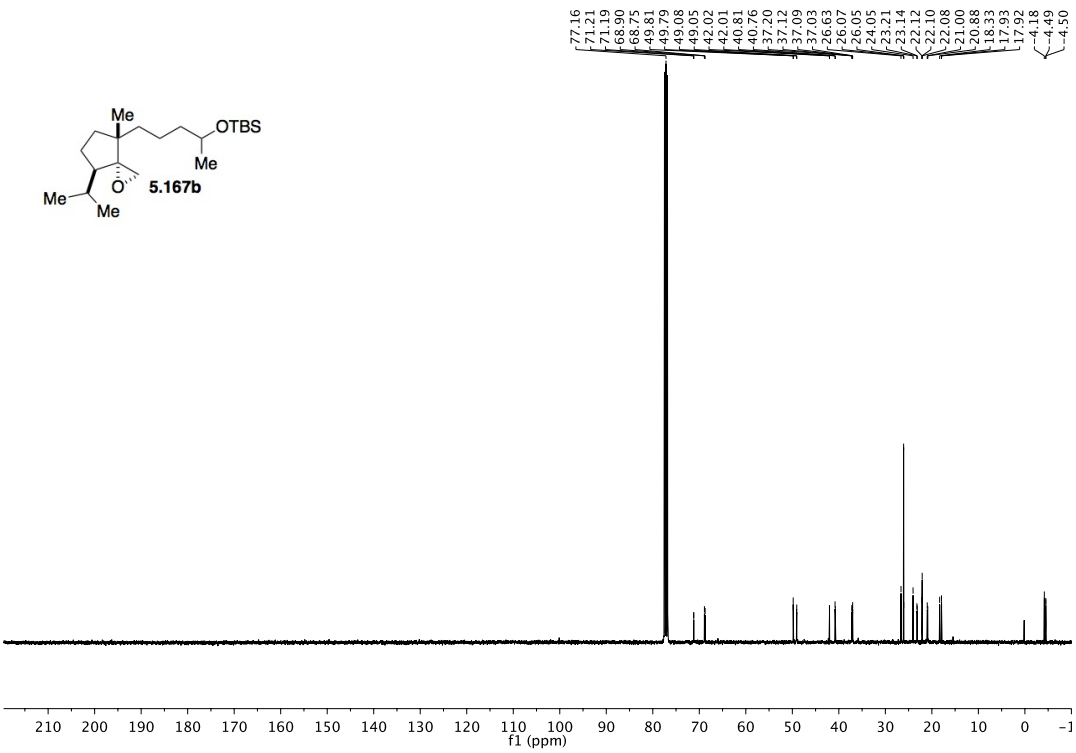

7.26
4.77
4.76
4.75
4.74
3.82
3.71
2.43
2.33
2.05
1.87
1.64
1.27
1.12
1.10
0.98
0.96
0.95
0.88
0.79
0.76
0.04
0.00
Me
OTBS
Me
Me
Me
5.166
4.00
2.01
1.94
1.98
20.19
6.30
5.88
6.02
18.16
6.12
11.93
f1 (ppm)

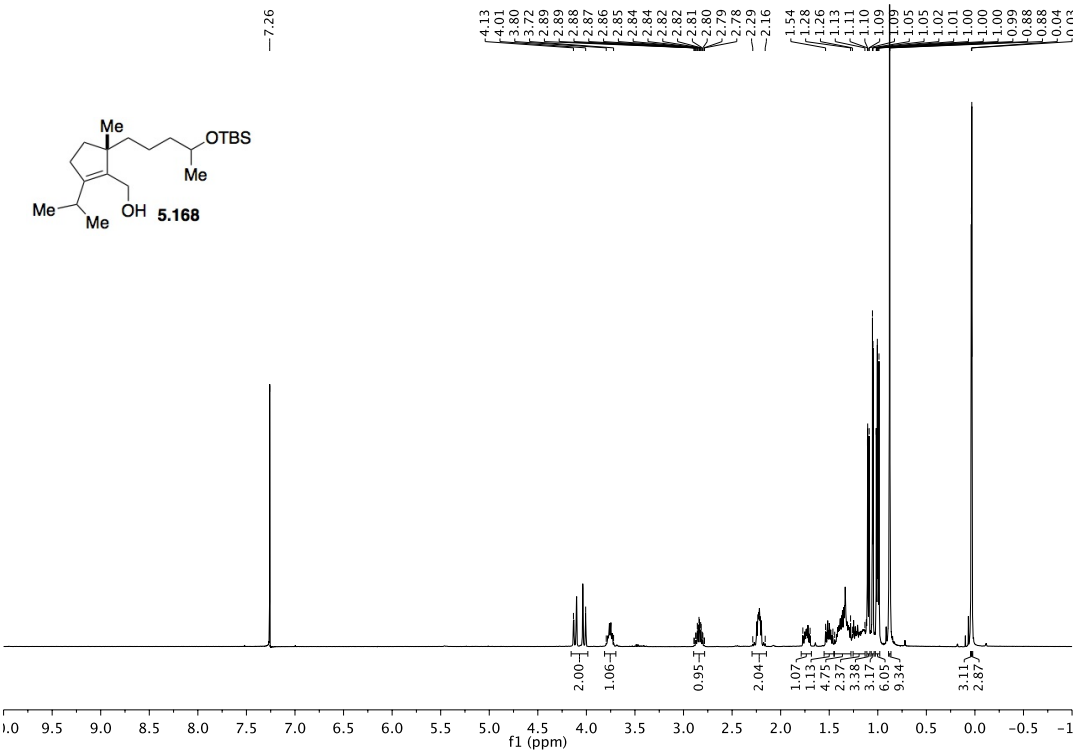

Me
OTBS
Me
Me
Me
5.166
163.19
163.14
103.14
77.16
68.96
68.85
51.35
51.29
46.07
42.32
42.22
40.78
40.74
37.17
37.12
28.97
28.94
27.38
27.29
26.07
24.09
24.05
23.25
22.12
21.34
18.33
16.70
0.16
-4.17
-4.20
-4.51
-4.54
f1 (ppm)


Me
OTBS
Me
O
Me
Me
5.167a
7.26
3.81
3.73
2.69
2.69
2.68
2.68
2.57
2.55
2.08
2.02
1.66
1.57
1.54
1.41
1.25
1.14
1.12
1.10
0.90
0.88
0.87
0.86
0.81
0.80
0.05
2.00
1.66
1.69
1.86
4.23
5.82
6.25
5.78
6.36
24.17
5.81
5.75
11.91
f1 (ppm)


Me
OTBS
Me
O
Me
Me
5.167a
77.16
69.93
69.88
68.79
68.76
48.83
48.78
47.23
47.11
42.65
40.79
40.76
39.69
39.62
36.33
36.23
26.49
26.07
26.05
24.14
23.99
23.34
23.30
22.81
21.10
20.97
20.74
20.54
19.40
18.31
-4.14
-4.18
-4.53
-4.54
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)


7.26
Me
OTBS
Me
O
Me
Me
5.167b
3.81
3.74
2.79
2.77
2.61
2.59
2.09
2.08
2.07
2.06
2.05
2.04
2.03
1.71
1.64
1.60
1.54
1.46
1.16
1.13
1.11
1.10
1.04
0.97
0.90
0.86
0.85
0.83
0.04
2.37
2.00
2.00
2.31
2.44
6.41
13.93
6.46
2.31
28.43
6.44
12.38
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)


Me
OTBS
Me
Me
O
Me
5.167b
77.16
71.21
71.19
68.90
68.75
49.81
49.79
49.08
49.05
42.02
42.01
40.81
40.76
37.20
37.12
37.09
37.03
26.63
26.07
26.05
24.05
23.21
23.14
22.12
22.10
22.08
21.00
20.88
18.33
17.93
17.92
-4.18
-4.49
-4.50
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)


Me
OTBS
Me
Me
OH
Me
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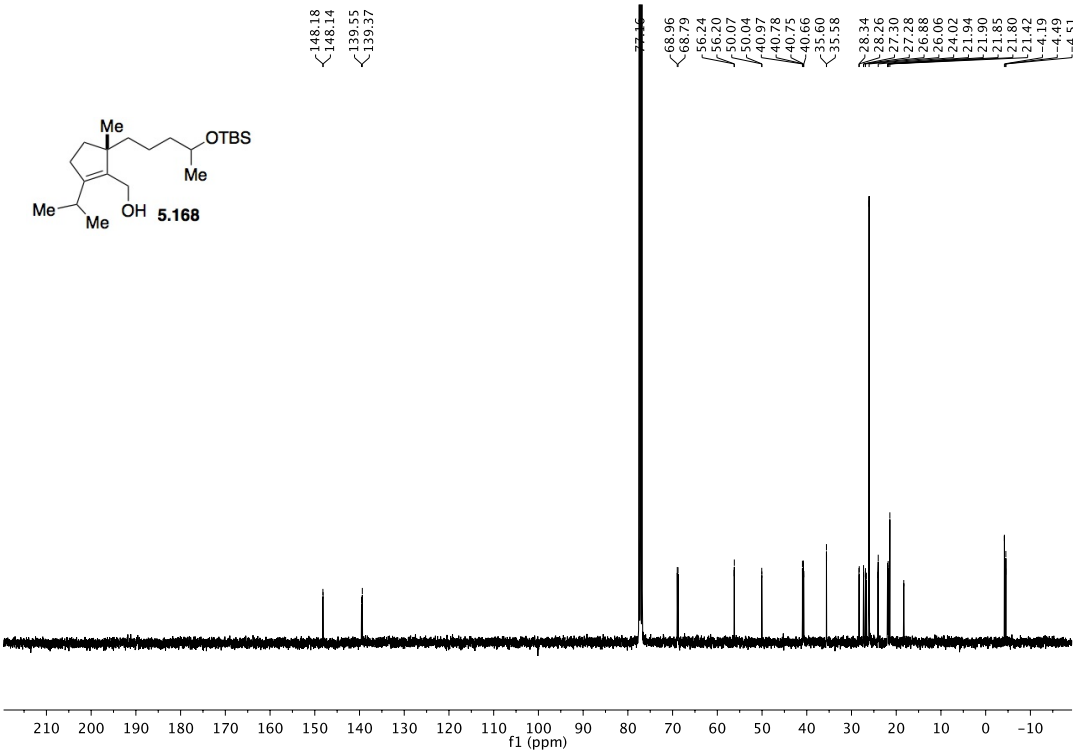
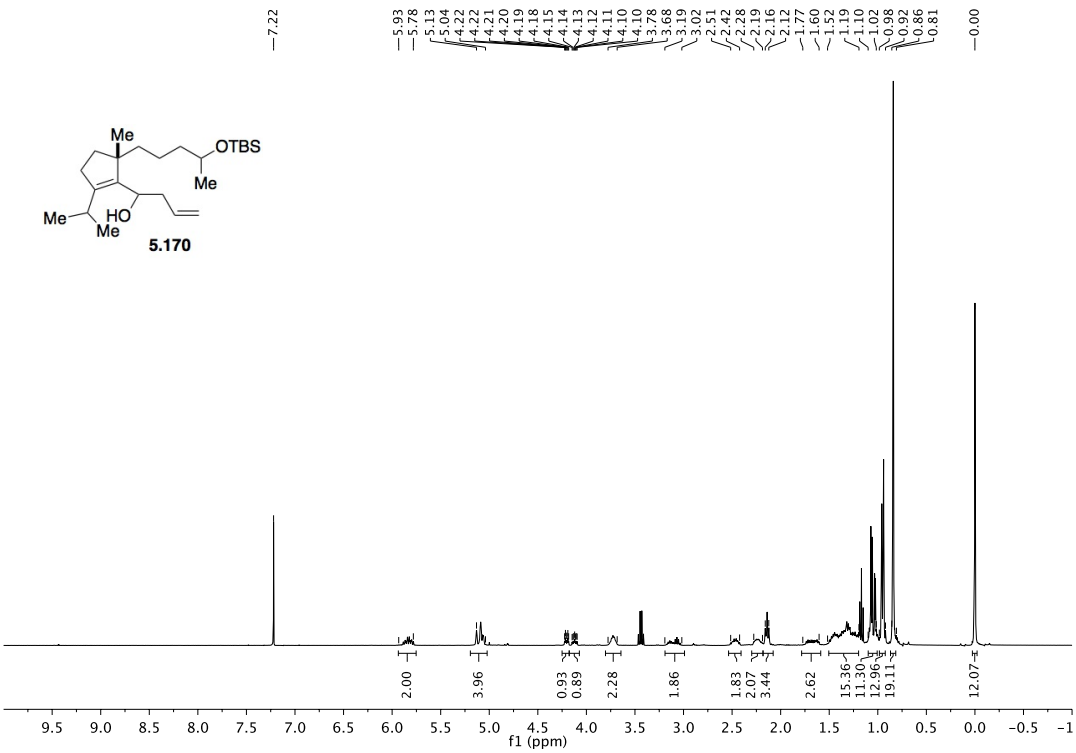
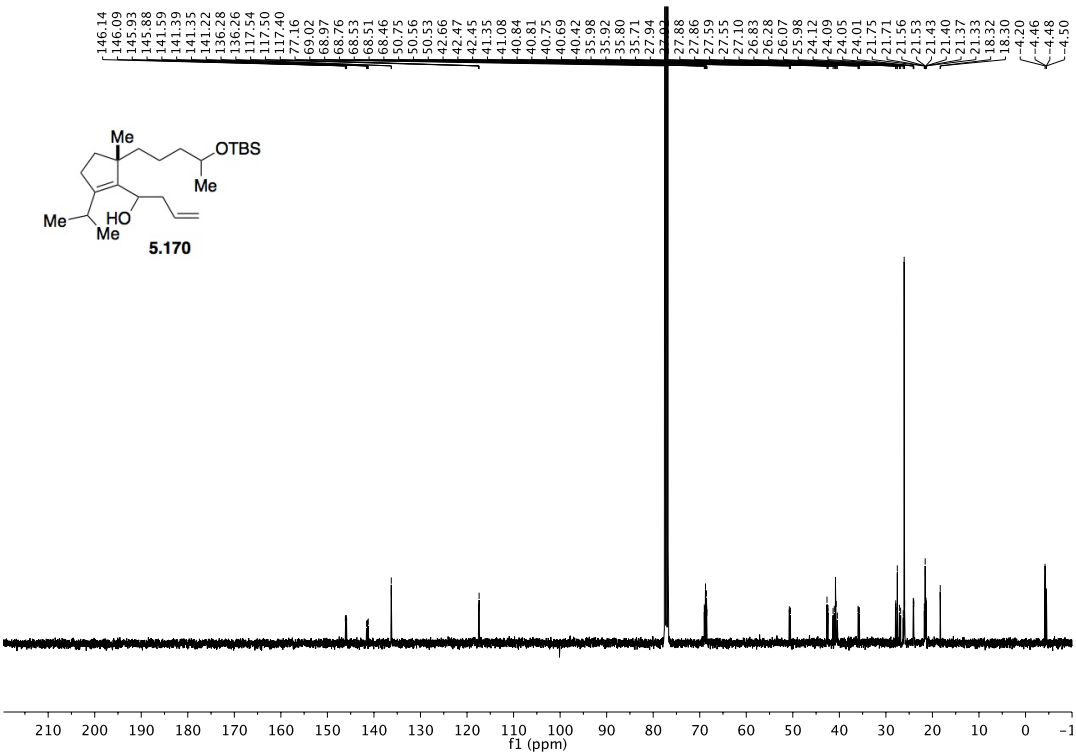
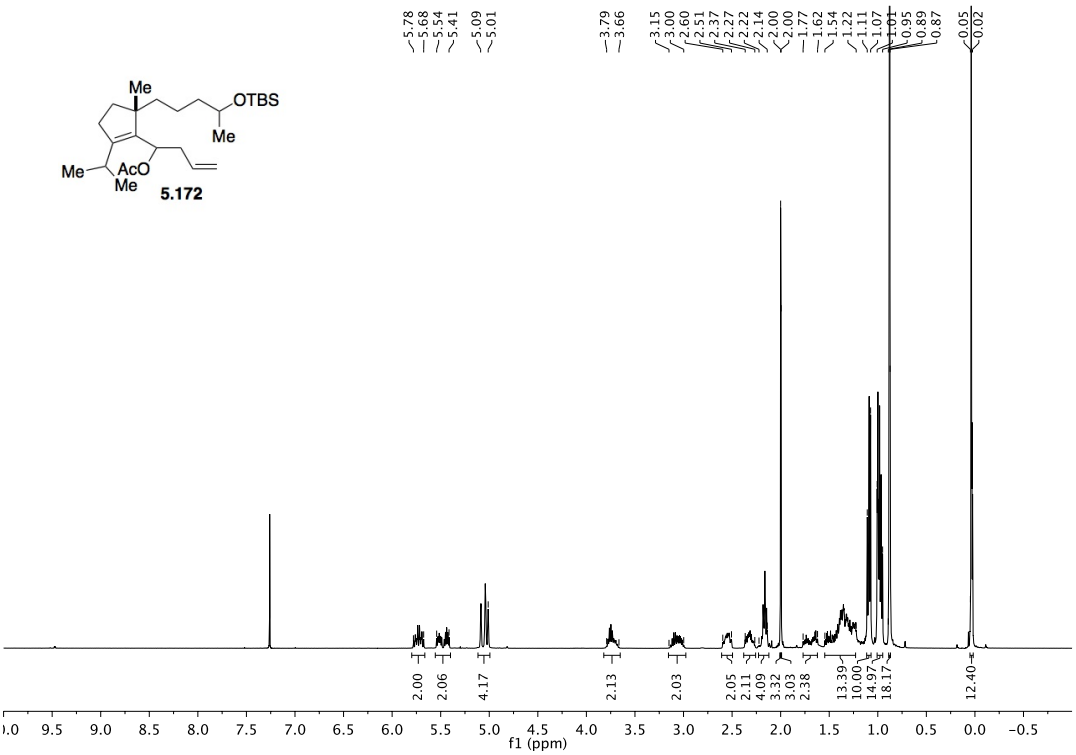
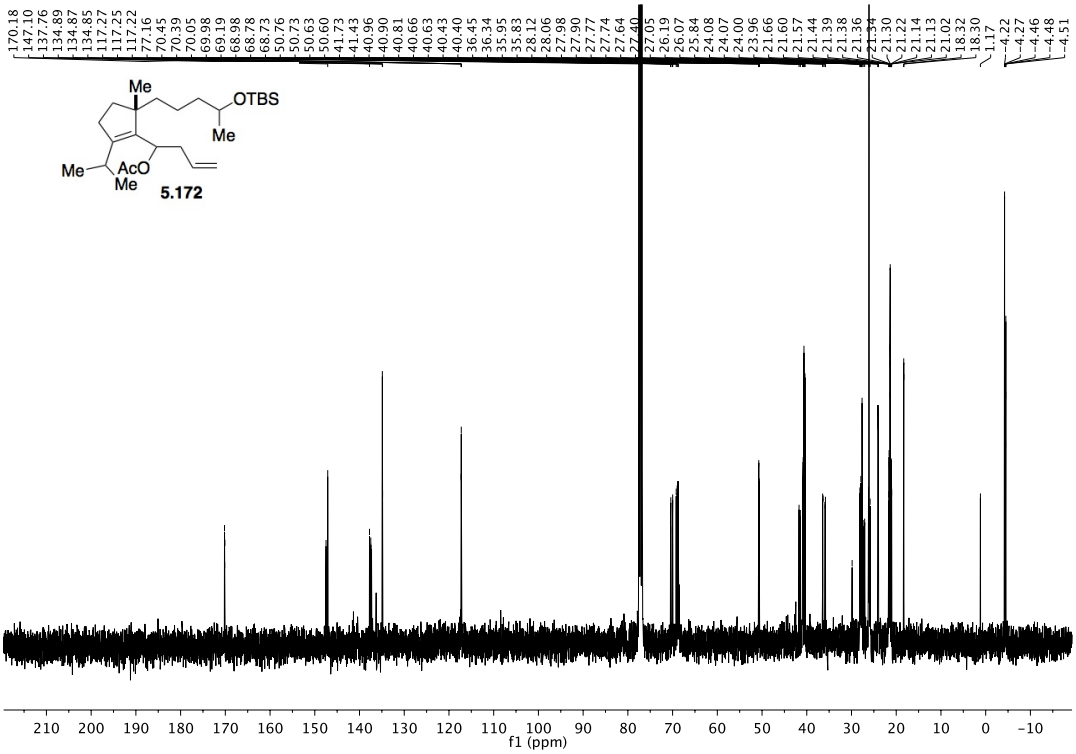
4.13
4.01
3.80
3.72
2.89
2.89
2.88
2.87
2.86
2.85
2.84
2.84
2.82
2.82
2.81
2.80
2.79
2.78
2.29
2.16
1.54
1.28
1.26
1.13
1.11
1.10
1.09
1.09
1.05
1.05
1.02
1.01
1.00
1.00
1.00
0.99
0.88
0.88
0.04
2.00
1.06
0.95
2.04
1.07
1.13
4.75
2.37
3.38
3.17
6.05
9.34
3.11
2.87
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


148.18
148.14
139.55
139.37
77.16
68.96
68.79
56.24
56.20
50.07
50.04
40.97
40.78
40.75
40.66
35.60
35.58
28.34
28.26
27.30
27.28
26.88
26.06
24.02
21.94
21.90
21.85
21.80
21.42
4.19
4.49
Me
OTBS
Me
Me
Me
OH
5.168
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.22
5.93
5.78
5.13
5.04
4.22
4.22
4.21
4.20
4.19
4.18
4.15
4.14
4.13
4.12
4.11
4.10
4.10
3.78
3.68
3.19
3.02
2.51
2.42
2.28
2.19
2.16
2.12
1.77
1.60
1.52
1.19
1.10
1.02
0.98
0.92
0.86
0.81
0.00
Me
OTBS
Me
Me
HO
Me
5.170
2.00
3.96
0.93
0.89
2.28
1.86
1.83
2.07
3.44
2.62
15.36
11.30
12.96
19.11
12.07
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


Me
OTBS
Me
Me
HO
Me
5.170
f1 (ppm)


Me
OTBS
Me
Me
AcO
Me
5.172
f1 (ppm)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147.10
137.76
134.89
134.87
134.85
117.27
117.25
117.22
77.16
70.45
70.39
70.05
69.98
69.19
68.98
68.78
68.73
50.76
50.73
50.63
50.60
41.73
41.43
40.96
40.90
40.81
40.66
40.63
40.43
40.40
36.45
36.34
35.95
35.83
28.12
28.06
27.98
27.90
27.77
27.74
27.64
27.40
27.05
26.19
26.07
25.84
24.08
24.07
24.00
23.96
21.66
21.60
21.57
21.44
21.39
21.38
21.36
21.34
21.30
21.22
21.14
21.13
21.02
18.32
18.30
1.17
-4.22
-4.27
-4.46
-4.48
-4.51
Me
OTBS
Me
Me
AcO
Me
5.172
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

8.4 Acknowledgments

I'm deeply thankful to my supervisor, *Prof. Dr. Karl Gademann*, for his passion and enthusiasm for complex and challenging natural products. His motivation and encouraging mentality was inspiring in every aspect of my PhD.

Prof. Dr. Andreas Pfaltz is deeply acknowledged for accepting the co-examination of my thesis as well as for the support concerning my future footsteps in chemistry.

I'm also grateful to *Prof. Dr. Christof Sparr* for chairing my defense and for helpful and fruitful discussions in any aspects of chemistry.

I'm thankful to our collaborators *Prof. Dr. Leo Eberl* and *Christian Jenul* (University of Zurich), *Dr. Marcel Kaiser* (Swiss Tropical and Health Institute Switzerland) and *Dr. Dominic Hoepfner* (Novartis Pharma AG) for the fruitful work at the frontiers of biology and chemistry. My dear colleague *Dr. Simon Sieber* is acknowledged for the help and support in the fragin project and for sharing his wisdom and awesome taste for excellent cheese and fantastic whisky with me.

Dr. Erika Crane, Dr. Regina Berg, Dr. Simon Sieber, Dr. Elias Kaufmann, Dr. Nadine Bohni, *Dr. Florian Huber, MSc Robin Wehlauch, MSc Manuel Scherer and MSc Vidya Mannancherril* are acknowledged for helpful input and corrections of this thesis.

I'm thankful to my highly talented students *Joel Rösslein* and *Vidya Mannancherril* for their significant synthetic contribution to this work. Furthermore, I'm especially proud of you that you continued to proceed in your own PhD-studies and I'm looking forward and of course expect from you high yields, excellent diastereomeric ratios as well as a fruitful work. On this behalf, I wish you only the best for your scientific careers.

I would like to especially thank all former and present members of the G*ademann group*. The senior PhDs who always had a critical look at the undergraduates and always gave good advices in chemistry but mostly on all social aspect and events, thanks to *Dr. José Gomes* (my mentor and outstanding chemist), *Dr. Patrick Burch* (I still got more hair than you), *Dr. Samuel Bader* (Mr. Wisdom), *Dr. Johannes Hoecker* ("if you can buy it, buy it"), *Dr. Malika Makhlouf* ("he always looks at scientific papers"), *Dr. Hideki Miyatake-Ondozabal* ("chin-chin"), *Dr. Suman de Sarkar* (so many T-shirts on the tree…) *Dr. Simon Sieber* (a good whisky is all you need), *Dr. Christophe Thommen* (the one with the real name), *Dr. Verena Grundler* ("finally done"), *Dr. Elias Kaufmann* ("I need that Spongebob") and Dr. Fabian Schmid (1 city 1 song). The current members of the Gademann group, *Dr. Erika Crane* ("Oh boy"), *Dr. Regina Berg* (Ms. Wisdom), *Dr. Nadine Bohni* (Miss analytics), *Manuel Scherer* (Mr. Beach Bar), *Robin Wehlauch* ("DnB 4 life"), *Isabel Kerschgens* (Miss Fado), *Simone Grendelmeier* (coyote), *Jan Hanusch* (Nafzger vo Wängi), *Hiromu Hattori* (work work work work work), *Dr. Chien-Chi Hsiao* (work work work work work), *Dr. Florian Huber* (Panini), *Raphael Liffert* (Mr. TGL), *Andrea Meier* (let the bacteria grow), *Ellen Piel* ("good morning in the morning"), *Joel Rösslein* (FTM) and *Mathieu Szponarski* (ham-man). I wish the current group members all the best for their scientific career and hope to see many publications from you.

I would like to especially highlight my all-time labmate *Manuel Scherer* for sharing all associated ups and downs in chemistry as well as his excellent taste for good music. On this behalf, reach for the moon, even if you miss it, you will land at the beach bar.

The members of the Sparr group, *Achim Link* (Starnberger See), *Dominik Lotter* (hair-brother)*, Christian Fischer* ("you can read this in my publication"), *Reto Witzig* (Thurgau), *Vincent Fäseke* (chocolate boy), as well as their mentor *Dr. Christof Sparr* for sharing the lab and all chemistry-based and not so chemistry-based discussions.

My scientific colleagues from the bachelor studies at the FHNW as well as from the University of Basel, especially *Ina Bodoky, Stefanie Geigle, Livia Glanzmann, Samantha Brianza, Natalie Huber, Cathrin Ertl, Annika Büttner, Daniel Ebner, Manuel Scherer, Philipp Raschle, Simon Glauser*, *Luca Schweighauser, Patrick Wilhelm, Martin Rother* and *Severin Sigg.*

The *Rhino–crew, Manuel Riedo, Rafael Sande, Marco Felder, Severin Giger and Timm Hettich,* are acknowledged for all the beautiful holiday trips in Europe, from drinking whisky in Scotland, all the friendly Hallo's we met in Budapest, as well as the amazing trip in Canada (I can't see any forests anymore) and the United States (what happens in Vegas, stays in Vegas). My personal highlight was our trip to Cuba. The astonishing scenery and the relaxed atmosphere (and of course the cigars, langoustes and daiquiris) will be unforgotten. Our fascinating trips could not be better described with the words: "Ça c'est bon pour la moral".

The *Chöpfli-crew* for spending a short but intense weekend in Munich with more forgotten than actually happened moments.

Meeting my friends from my beloved hometown gave me always-good flashbacks of beautiful and especially funny moments. Many thanks to the city of Bern (where my heart belongs) and my friends from this town, *Dominic Herren, Ramon Wymann, Riv Vakili, Alex Stöckli, Fabian Albertin, Fabian Lehmann* and *Christian Herren* for spending good times outside the laboratory.

Without the help for several analytical measurements, many results couldn't be realized. From the University of Basel: *Dr. Markus Neuburger, Dr. Heinz Nadig, Dr. Daniel Häussinger* and *Dr. Collin Morris. From Zurich: Prof. Dr. Oliver Zerbe* and his NMR-Team, *Dr. Anthony Linden* and the MS-service of *PD Dr. Laurent Bigler*, especially Miss *Jrène Lehmann* for chiral HPLC-measurements.

For the entire secretary-related paper work I would like to thank *Marina Mambelli-Johnson, Beatrice Erismann*, *Brigitte Howald (Basel)* and the *HR*-team of Zurich, as well as the technical staff from Basel who are keeping the building alive and in shape: *Markus Ast, Andres Koller, Andreas Sohler, Fabrice Cabrera, Manuel Hermida, Markus Hauri, Roy Lips* (Basel) and the *Werkstatt* team from Zurich.

I'm thankful to my parents Ginette and André, my brother Jérôme and my grandmother Selma for their support in all aspects of my PhD-studies.

My girlfriend Vidya, for her love, patience and support. Many things would not be possible without her warm attitude. Merci für aues mi Schatz. Always.